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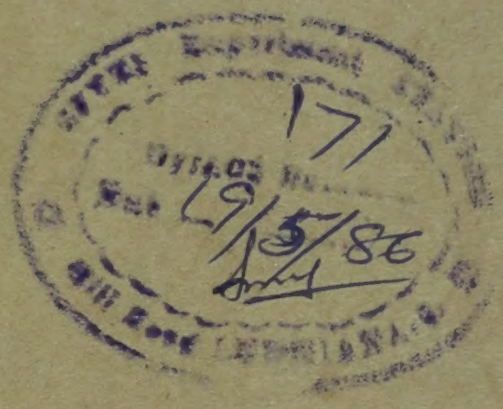

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Communications

A Novel Conversion of Narcotine into a Macrolide

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Received 13 *November* 1985; *accepted* 24 *January* 1986

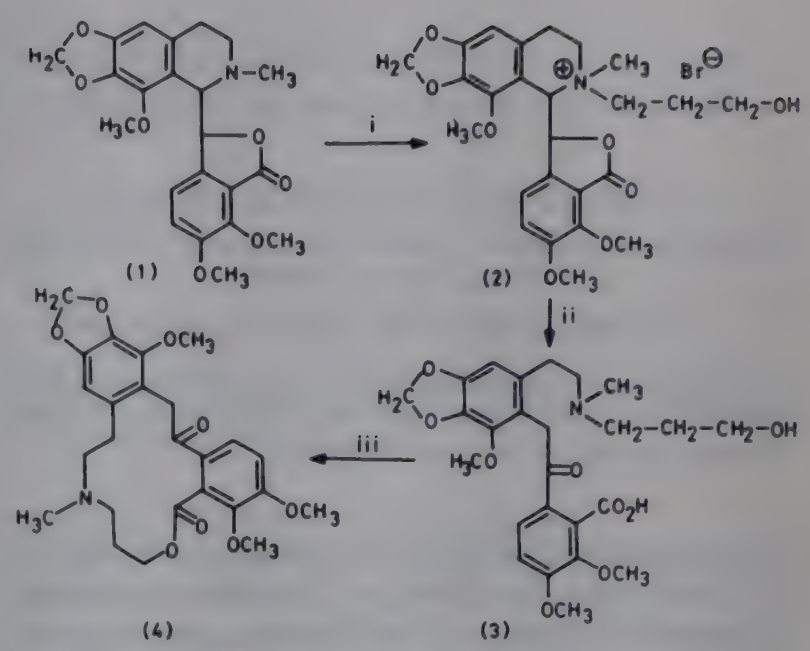
Narcotine (1) has been quaternized with 3-bromopropanol; the resulting compound (2) is treated with aqueous potassium hydroxide to give 3 which on lactonization with TsCl and triethylamine yields the 14-membered macrolide (4).

Morphine alkaloids have been subjected to various structural modifications in order to develop more potent, biologically active compounds[1]. Narcotine (1) which belongs to phthalideisoquinoline group, occurs to the extent of 0.7-6.4% in opium[2] and is one of the cheap by-products in opium industry.

We were interested to modify the structure of narcotine (1) in order to develop compounds having better pharmacological significance. Here, we report for the first time the conversion of 1 into a 14-membered macrolide (4) employing cheap reagents in a simple three-step process (Scheme 1).

Narcotine (1) was quaternized[3] with 3-bromopropanol and the quaternary salt (2) treated with aq. potassium hydroxide at reflux temperature for 1 hr to yield N-(3-hydroxypropyl)nor-narceine (3) in 80% yield; m.p. 102-5°; IR ($CHCl_3$): 3260 (OH), 2300-2500 (CO_2H) and 1680 cm^{-1} (Ar−C=O); PMR ($CDCl_3$): δ 1.6-2.1 (*m*, 2H, $-CH_2-CH_2-OH$), 2.6 (*s*, 3H, *n*-CH_3), 2.8-3.3 (*m*, 6H, $Ar-CH_2-CH_2-N-CH_2-$), 3.5-3.8 (*m*, 3H, $-CH_2OH$), 3.8 (*s*, 9H, $3\times OCH_3$), 4.3 (*s*, 2H, $Ar-CH_2-C=O$), 5.8 (*s*, 2H, $-O-CH_2-O-$), 6.3 (*s*, 1H, Ar−H), 6.8 (*d*, 1H, Ar−H), 7.3 (*b*, 1H, $-CO_2H$), 7.4 (*d*, 1H, Ar−H) (Found: C, 61.3; H, 6.3; N, 2.6. $C_{25}H_{31}NO_9$ requires C, 61.3; H, 6.4; N, 2.9%).

Various approaches are available for lactonization of ω-hydroxycarboxylic acids[4]. Attempts to lactonize 3 with cyanuric chloride, a reagent reported[5] for double activation, were unsuccessful and led to a complex mixture of unidentifiable products. Lactonization of 3 to 4 was achieved as follows: A dilute solution of 3 in chloroform (1.76 mmol/litre) was stirred with tosyl chloride and triethylamine at 50° for



i, $Br-CH_2-CH_2-CH_2-OH$; ii, aq. KOH; iii, TsCl and TEA.

Scheme 1

18 hr to afford 4 in 40% yield as a hygroscopic thick liquid; IR ($CHCl_3$): 1730 (lactone-C=O) and 1680 cm^{-1} (Ar−C=O); PMR ($CDCl_3$): δ 1.4-1.8 (*m*, 2H, $-CH_2-CH_2-O-$), 2.27 (*s*, 3H, N−CH_3), 2.4-2.7 (*m*, 6H, $Ar-CH_2-CH_2-N-CH_2-$), 3.6-3.85 (*m*, 2H, $-O-CH_2-$), 3.83 (*s*, 6H, $2\times OCH_3$), 3.93 (*s*, 3H, OCH_3), 4.2 (*s*, 2H, $-CH_2-CO-$), 5.83 (*s*, 2H, $-O-CH_2-O-$), 6.4 (*s*, 1H, Ar−H), 6.9-7.9 (*ABq*, 2H, Ar−H); *MS*: *m/z* 471 (M^+).

It is quite possible that the 4 may be biologically more active than the parent 1 on account of the presence of a 14-membered lactone ring. The present approach can open up ample scope for preparing various macrocyclic lactones from the naturally occuring phthalideisoquinoline alkaloids.

One of us (T S M) gratefully acknowledges the award of a research scholarship given by the Indian Institute of Science, Bangalore. The financial assistance from CSIR, India, is gratefully acknowledged.

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Pyridinium Bromochromate—A New Reagent for Bromination & Oxidation

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The new reagent, pyridinium bromochromate (PBC), apart from being efficient as an oxidant for alcohols, also functions as a good brominating agent for aromatic compounds.

A wide variety of chromium (VI) reagents are available in literature for the oxidation of alcohols to carbonyl compounds[1]. In view of the increasing importance of pyridinium chlorochromate (PCC)[2] and pyridinium fluorochromate (PFC)[3] in organic synthesis as potential, mild and selective oxidising agents an attempt was made to extend the study to other halochromates. Herein we introduce a new reagent, pyridinium bromochromate (PBC). Apart from being an efficient oxidant, PBC can also be used for bromination of aromatic compounds.

Thus anisole (**1a**), acetanilide (**2a**) and benzanilide (**3a**) when heated at 90-100° with 1.1 equivalent of PBC in acetic acid or chloroform gave the respective *p*-bromo derivatives (Table 1) in high yields. This is an unprecedented behaviour observed for the halogen-bond chromium (VI) reagents. However, the mode of bromination has been found to be quite different for the aromatic hydrocarbons such as anthracene (**4a**) and fluorene (**5a**) since these are readily converted into the corresponding 9,10-dibromoanthracene (**4b**) and 9-bromofluorene (**5b**) under the same conditions. Further PBC brominates acetophenones to afford ω-bromoacetophenones in fairly good yields. The results of the bromination studies are summarised in Table 1.

Analogous to PCC and PFC, PBC also oxidises alcoholic compounds such as benzyl alcohols (**11a**, **12a**), diphenylcarbinol (**13a**), fluoren-9-ol (**14a**), benzoin (**15a**) and benzpinacol (**16a**) to the corresponding carbonyl compounds in good yields, when they are refluxed in chloroform for 3 to 4 hr. The oxidation in dichloromethane was sluggish. The number of equivalents of PBC required for oxidation (1.2) is relatively less than that required for the other two reagents. Table 2 presents the results of PBC oxidation of alcohols.

Reactions with alicyclic alcohols, aliphatic primary and secondary alcohols and α,β unsaturated alcohols are not smooth. Detailed studies and the mechanistic aspects are under investigation.

Preparation of pyridinium bromochromate

A solution of chromium trioxide (20 g, 0.2 mol) in water (25 ml) was cooled to 0° and to this was added 47% hydrobromic acid (38 ml, 0.21 mol) slowly with vigorous stirring. Pyridine (16.2 ml, 0.2 mol) was then added dropwise during 15 min to afford a brown solid. The reaction mixture was cooled for 4 hr and the dark

Table 1—Bromination of Aromatic Compounds by PBC

Substrate	Product	Solvent	Time (hr)	Yield (%)
Anisole (**1a**)	4-Bromoanisole (**1b**)	HOAc	1	89
		$CHCl_3$	3	63
Acetanilide (**2a**)	4-Bromoacetanilide (**2b**)	HOAc	0.5	87
		$CHCl_3$	2	85
Benzanilide (**3a**)	4-Bromobenzanilide (**3b**)	HOAc	0.5	97
		$CHCl_3$	2	90
Anthracene (**4a**)	9,10-Dibromoanthracene (**4b**)	HOAc	0.5	84
		$CHCl_3$	1.5	60
Fluorene (**5a**)	9-Bromofluorene (**5b**)	HOAc	3	73
Acetophenone (**6a**)	ω-Bromoacetophenone (**6b**)	HOAc	4	40
3-Nitroacetophenone (**7a**)	3-Nitro,ω-bromoacetophenone (**7b**)	HOAc	8	50
4-Nitroacetophenone (**8a**)	4-Nitro-ω-bromoacetophenone (**8b**)	HOAc	8	51
3-Chloroacetophenone (**9a**)	3-Chloro-ω-bromoacetophenone (**9a**)	HOAc	8	30
4-Bromoacetophenone (**10a**)	4,ω-Dibromoacetophenone (**10b**)	HOAc	5	49

*Twice the amount of PBC is used.

Table 2—Oxidation of Alcohols by PBC[a]

Alcohol	Product	Time (hr)	Yield (%)
Benzyl alcohol (**11a**)	Benzaldehyde (**11b**)	3	78
2-Chlorobenzylalcohol (**12a**)	2-Chlorobenzaldehyde (**12b**)	3	95
Diphenylcarbinol (**13a**)	Benzophenone (**13b**)	3	83
Fluorene-9-ol (**14a**)	Fluoren-9-one (**14b**)	4	70
Benzoin (**15a**)	Benzil (**15b**)	3	91
Benzpinacol (**16a**)	Benzophenone (**13b**)	3	87

[a]Solvent chloroform

brown crystals obtained were filtered and dried *in vacuo*; yield 27.7 g (53%); m.p. 108°; IR (KBr): 1045, 1025, 950, 770, 670, 605, 383, 350, 260 and 230 cm^{-1}; UV: (H_2O): 347 (ε450); 255 (4240) and 204 nm (5740); *p*H of 0.03 *M* aq. solution 3.35; Λ_M: 110 mho cm^2 mol^{-1} (Found: C, 23.6; H, 2.3. Calc.: C, 23.1; H, 2.3%).

Bromination: General method

To a suspension of PBC (2.86 g, 0.011 mol) in acetic acid (12 ml), was added the substrate (0.01 mol) dissolved in a small amount of acetic acid. The reaction mixture was heated on a water-bath with occasional stirring and TLC monitoring. The completion of the reaction was also evidenced from change in the colour of the contents to green. The reaction mixture was poured into water (100 ml), extracted with ether, the ethereal extract washed with aq. $NaHCO_3$ and water, dried (Na_2SO_4), filtered and solvent removed. The product was purified by distillation or recrystallisation or column chromatography.

Oxidation of alcohols: General method

To PBC (3.12 g, 0.012 mol) in chloroform was added the alcohol (0.010 mol) dissolved in small amount of the solvent and heated under reflux for 3 to 4 hr with TLC monitoring. After completion ether was added to the reaction mixture and the ether extract passed through a column of silica gel. Evaporation of the solvent furnished the product which was isolated as a 2,4-dinitrophenylhydrazone.

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Synthesis of Cairomycin-B, a Novel Bicyclic Peptide Containing Lysine & Aspartic Acid

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Cairomycin-B, a bicyclic peptide antibiotic containing lysine and aspartic acid has been synthesised. Diketopiperazine (**5**) is first prepared from the compound (**3**), deprotected and subjected to internal cyclisation using DCC and N-hydroxy-succinimide to yield the title compound (**7**) in 11% yield. All the intermediates and final compound have been fully characterised.

Recently Shimi and coworkers have isolated three antibiotics, designated as cairomycins A, B and C, from the fermentation broth of streptomyces AS-C-19, which was isolated from the soil samples collected from Cairo area. Based primarily on physicochemical, analytical and spectral data these workers reported the structures of cairomycin-A[1] and cairomycin-B[2]. Cairomycin-B, the major component of the extract was shown to have a bicyclic dipeptide structure (**7**) containing lysine and aspartic acid as the constituent amino acids. In this paper we wish to report the synthesis of cairomycin-B.

The suggested structure **7** of cairomycin-B contains a six-membered diketopiperazine ring and an eleven-membered ring arising from the internal cyclisation between the side chains of aspartic acid and lysine. Starting from a suitably protected dipeptide of lysine and aspartic acid, the target molecule can be built by building the diketopiperazine ring first followed by deprotection of the side chain protecting groups and intramolecular cyclisation. The other alternative would involve a reversal of the order in which the two rings would be formed. A molecular model of **6** indicates that the side chains in diketopiperazine are free and lie close enough to form the eleven-membered ring through internal cyclisation involving the side chain functional groups.

Since both the cyclisations involve the formation of an amide bond between two different sets of amino and carboxyl groups, a successful synthesis would require satisfactory orthagonal protection for these group in the protected dipeptide (**3**). The details of protecting group and synthetic plan are outlined in Scheme 1.

N^{α}-*t*-Butoxycarbonyl-N^{ε}-benzyloxy-carbonyl-L-lysine (**1**) and aspartic acid dibenzyl ester *p*-toluenesulphonate (**2**) were prepared following standard procedures[4,5]. N^{α}-*t*-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-aspartic acid dibenzyl ester (**3**) was prepared in 75% yield by coupling of **1** and **2** mediated by dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide in dichloromethane. Dipeptide (**3**) was selectively deprotected at the N-terminal using anhydrous trifluoroacetic acid (TFA) in 76% yield which readily gave the corresponding diketopiperazine (**5**) in 56% yield on internal cyclisation[6,7]. N^{ε}-Benzyloxycarbonyl and β-benzyl ester protections in **5** were removed by anhydrous hydrogen bromide in glacial acetic acid (32% HBr in HOAc) in 95% yield. DCC and N-hydroxysuccinimide were employed to effect the formation of eleven-membered ring. The cyclisation reaction was done in high dilution in pyridine for 3 days. Column chromatography of the reaction product followed by preparative TLC on silica gel gave the target compound (**7**) in 11% yield as colourless crystalline solid.

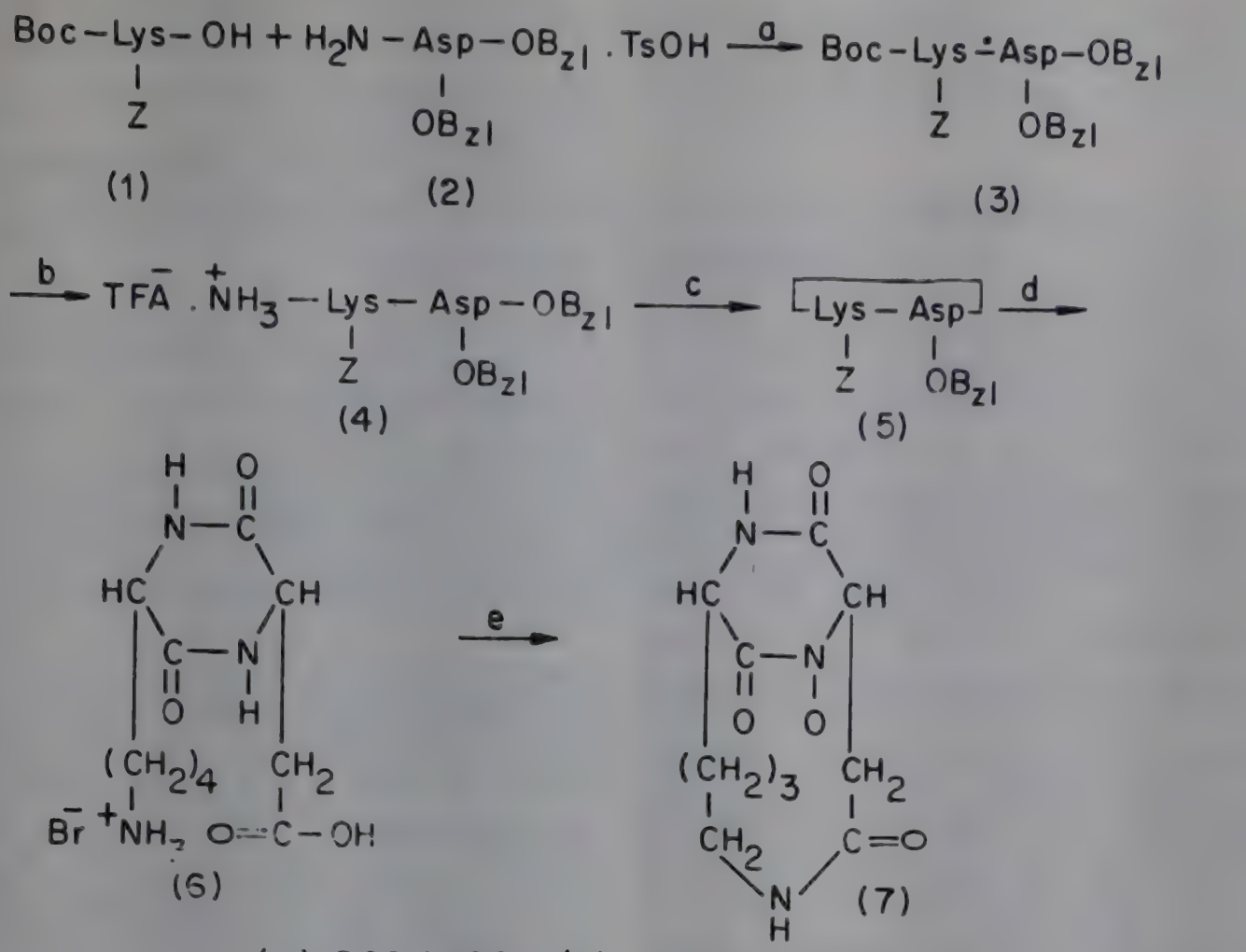
Synthetic compound **7** showed similar physico-chemical and biochemical characteristics as reported by Shimi *et al.*[2] except for some differences in IR, UV and physical appearance. These differences may be attributed to some minor impurities in the natural compound.

Experimental Procedure

Amino acids (Sigma Chemicals) were used as such. All the solvents used were of reagent grade and fractionally distilled before use.

Melting points were determined on a Kofler hot bench melting point apparatus and are uncorrected. The infrared spectra of the compounds were recorded in KBr or nujol on a Perkin-Elmer 621 grating infrared spectrophotometer. PMR spectra were recorded on Perkin-Elmer R-32 (90 MHz) and Jeol FX-200 (200 MHz) spectrometers. Mass spectra, elemental analyses and optical rotations were obtained from Central Drug Research Institute. Lucknow.

TLC was performed on silica gel plates using the



(a) DCC/HOSu (b) TFA in CH_2Cl_2 (c) TEA (pH 8)

(d) HBr/HOAc (e) DCCI/HOSu (6 equiv.)

Scheme 1

following solvent systems: (A) Bu^nOH-AcOH-H_2O (4:1:1); (B) $CHCl_3$; (C) CH_3OH-$CHCl_3$ (1:9); (D) EtOAc (1 volume) and pyridine-AcOH-H_2O (20:6:11) (4 volumes) and (E) petrol-$CHCl_3$ (1:1). Spots were detected either by 1% ninhydrin solution in acetone, iodine vapours or chlorine/starch/potassium iodide (Rydon's reagent).

N^{α}-t-Butoxycarbonyl-N^{ε}-Benzyloxycarbonyl-L-lysine (**1**)

N^{ε}-Benzyloxycarbonyl-L-lysine, prepared from L-lysine hydrochloride by the method of Costopangiotis *et al.*[3], was converted into **1** by the reaction of di-*t*-butyl dicarbonate in 99.3% yield.

L-Aspartic acid dibenzyl ester p-toluenesulphonate (**2**)

It was prepared in 85% yield from L-aspartic acid by the method of Zeravas *et al.*[5].

N^{α}-t-Butoxycarbonyl-N^{ε}-benzyloxycarbonyl-L-lysyl-L-aspartic acid dibenzyl ester (**3**)

Compound (**1**, 2.65 g, 6.97 mmol), N-hydroxysuccinimide (0.80 g, 6.97 mmol) and DCC (1.44 g, 6.97 mmol) were added in ice cold dichloromethane (35 ml) and stirred for 10 hr with L-aspartic acid dibenzyl ester (prepared from 3.38 g, 6.97 mmol of **2** with 0.98 ml, 6.97 mmol of triethylamine). The reaction mixture was filtered and the filtrate successively washed with saturated aq. sodium bicarbonate, citric acid (0.7 *M*) and with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallised from ethyl acetate-pet. ether to give protected **3** (3.53 g, 75%). m.p. 110°; $[\alpha]_D^{25}$ −20.9 (*c*, 0.437, dimethylformamide); R_f(A) 0.69, R_f (C) 0.63, R_f (D) 0.90; PMR ($CDCl_3$): 7.5 (*m*, 3H, 3 × NH), 7.25 (*s*, 15H, 3 × $-C_6H_5$), 5.15 (*s*, 6H, 3 × $-CH_2-C_6H_5$), 4.85 (*m*, 1H, $-\alpha-CH$), 4.1 (*m*, 1H, $\alpha-CH$), 3.1 (*br*, 2H, Lys $\varepsilon-CH_2$), 2.9 (*br*, 2H, $-CH_2-CO$), 1.9-1.6 (*br*, 2H, Lys CH_2), 1.4 (*s*, 13H, $(CH_3)_3$ C- and Lys γ-CH_2 & δ-CH_2); IR (nujol): 1725, 1680, 1640 and 1520 cm^{-1} (Found: C, 65.6; H, 6.7; N, 6.3. $C_{37}H_{45}N_3O_9$ requires C, 65.8; H, 6.7; N, 6.2%).

N^{ε}-Benzyloxycarbonyl-L-lysyl-L-aspartic acid dibenzyl ester trifluoroacetate (**4**)

The ester (**3**, 3.17 g, 4.7 mmol) was treated with anhydrous trifluoroacetic acid (1 ml) at 0° C and left at room temperature for 20 min. Excess TFA was removed, the residue repeatedly washed with dry ether and dried over KOH pellets *in vacuo*, yield 2.5 g (76%), m.p. 108 ; $[\alpha]_D^{25}$ −8.7 (*c*, 0.467, dimethylformamide); R_f

(A) 0.60, R_f (C) 0.22, R_f (D) 0.66; IR (KBr): 1725, 1680 and 1520 cm^{-1} (Found: C, 58.9; H, 5.6; N, 5.9. $C_{33}H_{37}N_3O_7$. CF_3COOH requires C, 59.2; H, 5.6; N, 6.1%).

Cyclo (*L-lys(Z)-L-Asp(OBzl)*) (**5**)

Compound (**4**, 2.15 g, 3.06 mmol) was taken up in dichloromethane (20 ml) and triethylamine was added to it to bring the *p*H of the solution to **8**, and the mixture stirred at room temperature for 30 hr. The solid which separated out was filtered, washed with dichloromethane and dried. The filtrate was refluxed under stirring. The solid so obtained was filtered and washed again with dichloromethane. The process was repeated till no more solid appeared. Total yield of **5** was 0.8 g (56%), m.p. 182-84°; $[\alpha]_D^{25}$ −22.7 (*c*, 0.5, dimethylformamide); R_f (A) 0.46, R_f (C) 0.52; PMR ($CDCl_3$ + a drop of TFA): 7.3 (*s*, 10H, 2× $-C_6H_5$), 7.1-6.9 (*br*, 1H, $-CO-NH$), 6.8 (*s*, 1H, $-CO-NH$), 5.15 and 5.1 (*d*, 4H, J=6 Hz, 2× $-CH_2-C_6H_5$), 4.7-4.4 (*m*, 1H, α-CH), 4.2-4.0 (*m*, 1H, α-CH), 3.2 (*br*, 2H, Lys ε-CH_2), 3.0 (*br*, 2H, $-CH_2-CO$), 2.0-1.7 (*br*, 2H, Lys β-CH_2), 1.5 (*br*, 4H, Lys γ-CH_2 & δ-CH_2); IR (nujol): 1730, 1680, 1620 and 1520 cm^{-1} (Found: C, 64.7; H, 6.5; N, 8.7. $C_{25}H_{29}N_3O_6$ requires C, 64.2; H, 6.3; N, 9.0%).

Cyclo (*L-Lys-L-Asp*) *hydrobromide* (**6**)

The benzyl ester (**5**, 0.61 g, 1.31 mmol) was treated with HBr/acetic acid at room temperature for 6 hr. The reaction was followed by TLC and the excess HBr/acetic acid was removed *in vacuo*. Residue was triturated with dry ether and the hydrobromide salt filtered, washed with dry ether and dried over KOH pellets *in vacuo*, yield 0.4 g (95%), m.p. 252-54°; $[\alpha]_D^{25}$ −24.1 (*c*, 0.5, dimethylformamide); R_f (A) 0.18; IR (nujol): 1670 and 1450 cm^{-1}.

Cairomycin B (**7**)

The hydrobromide salt (**6**, 0.3 g, 0.975 mmol) was taken in dry pyridine (600 ml) and to this were added N-hydroxysuccinimide (1.8 g, 15.6 mmol), DCC (3.2 g, 15.6 mmol) and triethylamine (0.137 ml, 0.975 mmol) and the mixture was stirred for 73 hr. Glacial acetic acid (3 ml) was added and stirring continued for 20 min. Dicyclohexylurea that separated out was filtered off and the filtrate concentrated *in vacuo*. The residue was taken in ethyl acetate (200 ml), washed with water (2 × 10 ml) and dried (Na_2SO_4). Removal of ethyl acetate gave a residue that showed several spots on TLC in solvent system C which were ninhydrin negative and were visualised by Rydon's reagent. The residue was subjected to chromatographic separation on silica gel (column 2.5 × 40 cm^2) with pet. ether containing increasing volumes of chloroform. The fractions that were eluted with chloroform-pet. ether (1:1) were pooled together, concentrated and further subjected to preparative TLC over silica gel to give a colourless crystalline compound (24 mg, 11%), m.p. 123-24° (lit.[2], m.p. 120-21°), $[\alpha]_D^{27}$ −15.2 (*c*, 0.25, dimethylformamide); R_f (B) 0.49, R_f (C) 0.60, R_f (E) 0.30; PMR ($CDCl_3$): 7.15-6.9 (*br*, 1H, $-CO-NH$), 6.8 (*s*, 1H $-CO-NH$), 5.0 (*s*, 1H, $-CO-NH-CH_2$), 4.35 (*s*, 1H, α-CH), 4.2-3.9 (*br*, 1H, α-CH), 3.8-3.2 (*m*, 4H, overlapped on a doublet centred at 3.4 for Asp CH_2-CO and ε-CH_2), 2.0-1.5 (*m*, 4H, Lys 2× $-CH_2$), 1.2 (*s*, 2H, Lys CH_2); IR (nujol): 1680 and 1440 cm^{-1}; MS: *m/z* 225 (M^+) (Found: C, 53.5; H, 6.5; N, 18.3. $C_{10}H_{15}N_3O_3$ requires C, 53.3; H, 6.7; N, 18.7%).

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Some Interesting Sesquiterpenoids from *Sphaeranthus indicus* Linn. (Compositae)

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Three closely related, new hydroxy lactones (**1**, **2**, and **3**) have been isolated from the plant *Sphaeranthus indicus* Linn. via adduct formation with morpholine (in the case of **1** and **2**). Their structures have been determined on the basis of chemical and spectral evidences and correlation with a known trienelactone (**5**), derived from santonin. Two of these, **1** and **2**, contain an α-methylene-γ-lactone moiety and **3** contains a methyl group in place of the methylene group.

The plant *Sphaeranthus indicus* Linn. (Compositae) is reputed to have therapeutic properties and has found use in the indigenous system of medicine[1,2], thus warranting a chemical examination.

Exhaustive extraction of the air-dried, powdered, flower tops of the plant with hexane and chloroform in succession at room temperature and removal of the solvents at $40\pm2^{\circ}C$ under reduced pressure gave extractives in 4.7 and 2.0% yields respectively. Column chromatography of the hexane fraction on silica gel yielded straight chain compounds and a steroidal alcohol. The chloroform extract was found to contain three crystalline sesquiterpene lactones (**1**, **2** and **3**), all with an unusually located tertiary hydroxyl group. Two of the lactones (**1** and **2**) also contained α-methylene-γ-lactone moiety and the third (**3**) was a saturated lactone with a methyl group. The lactonic mixture after initial purification through chromatography was treated with morpholine, when **1** and **2** characteristically formed crystalline Michael amine adducts, whereas **3** did not. The reaction products after chromatography yielded **3** and the morpholine adducts of **1** and **2**, from which the two parent lactones were quantitatively regenerated via formation of the methiodides followed by treatment with mild alkali[3,4].

Structure and stereochemistry of **1**

The lactone (**1**), the major constituent, was a white crystalline solid, and exhibited in its IR spectrum bands at 3625, 1760, 1260, 1135, 940 and 800 cm^{-1} suggesting the presence of an α-methylene-γ-lactone moiety[5,6] and a hydroxyl group. The nature of conjugation was apparent when the spectra of **1** and its dihydro derivative (**4**) were compared. As expected, the UV spectrum of **1** exhibited absorption at 211 nm (ε 13, 370).

In conformity with its structure, **1** exhibited PMR (δ) signals due to a tertiary methyl (1.08, 3H, *s*) and a methyl on a tetrasubstituted double bond (1.78, 3H, *s*), in addition to sharp signals (5.84, and 6.24, 1H each, *s*) attributable to the exomethylene protons. The presence of these, and the absence of any signal due to vinylic proton, indicated a $\Delta^{4,5}$-eudesmane skeleton for **1**. The absence of signals between 3.6 and 4.1 was indicative of the tertiary nature of the hydroxyl group. The signal at 1.08 due to the tertiary methyl did not show any shift in pyridine[7], indicating that the hydroxyl was not on the carbon carrying the methyl group. The sharp singlet nature of the signals for the C-13 exomethylene protons indicated absence of allylic proton at C-7, presumably due to the presence of a hydroxy group at the position. The same inference was drawn from the singlet nature of the C-6 proton signal (5.1).

The mass spectrum was significant in that it did not show a M − 18 peak, but showed the M − 15 and M − 33 peaks, the latter arising due to the loss of a methyl and water molecule.

Confirmation of the structure of **1** was obtained in the following way. On catalytic hydrogenation in ethanol[8] over PtO_2 it absorbed one mol of hydrogen to give a crystalline dihydro-γ-lactone (**4**). The νC − O band of the parent lactone (**1**) at 1135 cm^{-1} shifted to higher wavenumber ($\Delta\nu = 35$ cm^{-1}) and appeared at 1170 cm^{-1} in **4**. The band at 800 cm^{-1} in **1** disappeared completely in **4**, showing clearly the presence of an α-methylene-γ-lactone moiety in **1**.

The PMR spectrum of **4** displayed signals due to C-10 methyl (1.04, 3H, *s*), C-4 methyl (1.79, 3H, *s*) and C-6 proton (4.97, 1H, *s*). The spectrum did not reveal the two lowfield singlets present in **1** but instead exhibited a doublet (1.18, 3H, $j=3$ Hz) attributable to the

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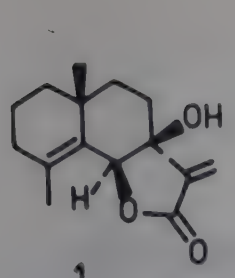

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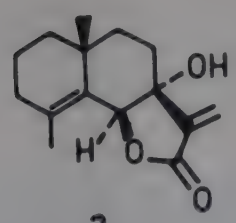

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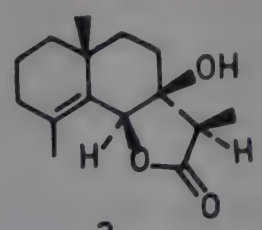

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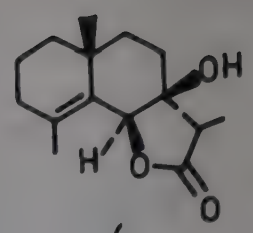

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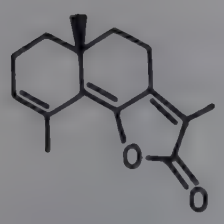

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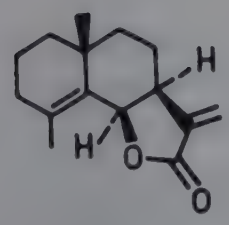

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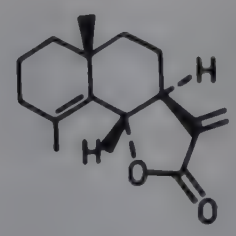

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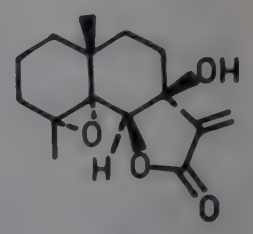

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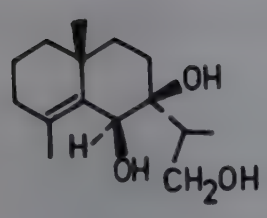

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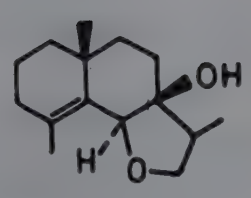

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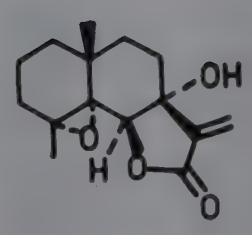

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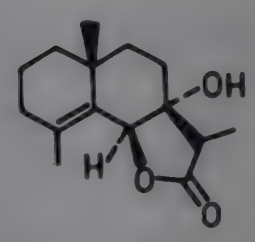

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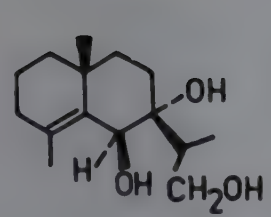

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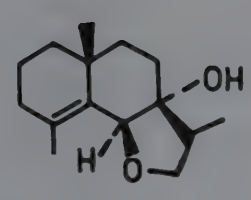

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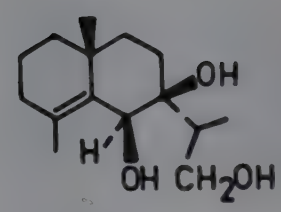

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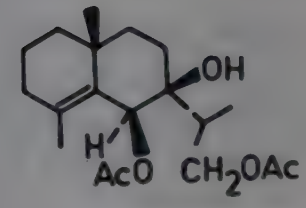

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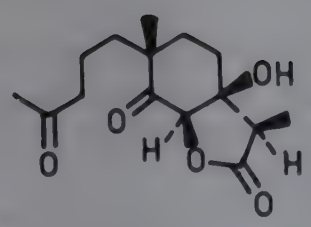

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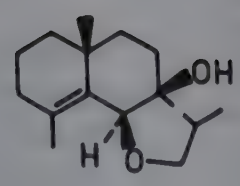

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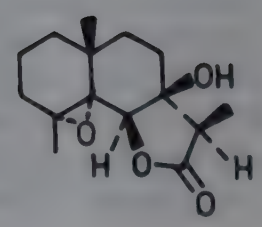

19

secondary C-11 methyl. Correspondingly, the C-11 proton appeared as a quartet only (2.76, 1H, $J = 3$ Hz). This again confirmed the blocking of the C-7 position.

The mass spectrum of **4** also did not show a M − 18 peak but the M − 15 and M − 33 peaks were significant.

Treatment of **4** with $POCl_3$ and pyridine resulted in a mixture of products, from which via chromatography an unexpected but conspicuous, known, trienelactone (**5**), with high laevorotation was obtained and characterised. It showed UV absorption at 330 nm (ε 20093). The PMR spectrum of **5** exhibited C-10, C-11 and C-4 methyls as singlets at 1.13, 1.90 and 2.16 respectively. A singlet at 5.82 was assigned to the C-3 proton. In addition, multiplets (centered around 1.70 and 2.75) were also observed. The m.p., rotation, and PMR spectrum of **5** were identical with those reported for the trienelactone previously obtained by McMurry

and Rane[9,10] from a santoninic acid derivative. This confirmed the presence of eudesmane skeleton, C-7 hydroxyl group, and C-6, C-7 locking up by the lactone moiety in **1**. Resistance towards hydroxylation by oxymercuration-demercuration again indicated the presence of tetrasubstituted double bond in **1**.

Similarity of the chemical shift of the C-10 methyl protons in **1** and those of the model compounds (**6**) and (**7**) (β-stereochemistry) indicated[11-13] that the C-10 methyl in **1** had β-stereochemistry. The stereochemistry at C-6, C-7 juncture was determined as follows: The lactone (**1**) on treatment with 1 mol of perbenzoic acid at 0° in chloroform yielded a crystalline monoepoxide (**8**), which exhibited in its IR spectrum bands at 3410, 1760, 1650, 1450, 1260, 1130, 975, 950 due to α-methylene-γ-lactone moiety and a hydroxyl group. The bands at 1000, 900 and 800 cm^{-1} were attributed to the epoxide function. Its UV spectrum showed an absorption maximum at 214 nm (ε 6759). As expected, the PMR spectrum displayed signals due to C-10 methyl (1.12, 3H, *s*), C-4 methyl (1.4, 3H, *s*), C-13 exomethylene protons (5.9 and 6.3 1H each, *s*). The C-6 proton signal was shifted upfield by δ 1.1 (4.0, 1H, *s*). The corresponding signal in the parent lactone was seen at 5.1. This observed shift was compared with those reported for (−)-frullanolide (**6**) and (+)-arbusculin-B (**7**) and their epoxides. The magnitude of the shift was comparable with the shifts reported for **6** and its epoxide. Therefore, by analogy the C-6 proton in **1** was inferred to be α.

The stereochemistry of the C-7 hydroxy group was concluded to be β since the lactone (**1**), in its IR spectrum (0.5 *M*, 5 cm cell, dil. soln. in CCl_4) did not show any strong internal OH-π hydrogen bonding[14]. This was further confirmed from the IR spectrum of **4** taken in solution under similar condition.

Compound (**4**) on reduction with lithium aluminium hydride (LAH) gave a crystalline triol (**9**). In the PMR spectrum of **9** the C-6 proton again appeared as a singlet at 4.66. An interesting feature of the PMR spectrum of **9** was the non-equivalence of C-12 hydrogens, each appearing as a double doublet at 3.66 ($J_{AB}=1.4$ Hz, $J_{BC}=4$ Hz) and 4.8 ($J_{AB}=1.4$ Hz, $J_{BC}=4$ Hz) respectively due to vicinal and geminal couplings. Besides, the signals due to C-4 methyl (1.75, 3H, *s*), C-10 methyl (1.2, 3H, *s*) and C-11 methyl (1.52, 3H, *d*, $J=4$ Hz) were also observed. The slight downfield shift observed for C-10 methyl was probably due to the axial hydroxyl function at C-6.

The triol (**9**) on treatment with *p*-toluenesulphonyl chloride and pyridine did not give any tosyl derivative, instead the oxide (**10**) was obtained, on prolonged heating on a water-bath. It showed expected PMR signals: C-11 methyl (1.00, 3H, *d*), C-10 methyl (1.17, 3H, *s*), C-4 methyl (1.79, 3H, *s*), C-6 proton (4.47, 1H, *s*). The sluggishness of the reaction further pointed to the relative stereochemistry of the C-6 hydroxy and the C-7 isopropyl group as being *trans* in **9**.

Structure and stereochemistry of **2**

The lactone (**2**), a white crystalline solid, was obtained as a minor constituent. Its IR, UV and PMR spectra closely resembled those of **1** from which it was inferred that it had the same gross structure as that of **1**.

The signal of the C-6 proton in the PMR spectra of **2** and of its various derivatives such as the monoepoxide (**11**), dihydro derivative (**12**), triol (**13**) and oxide (**14**) were closely similar to that of **1** and its corresponding derivatives. It was, therefore, concluded that the C-6 stereochemistry is the same in both. In its IR spectrum (0.5 *M*, 5 cm, cell, dil soln. in CCl_4), **2** exhibited a band at 3640 cm^{-1} which could arise only due to an axial hydroxyl[15]. This was confirmed from the indication of sufficient internal OH...π bonding in its IR spectrum (0.5 *M*, 5 cm cell, dil soln in CCl_4) and also in its dihydro derivative (**12**). Hence, it was concluded that **2** is only a C-7 hydroxy epimer of **1**.

The triol (**13**) on treatment with *p*-toluenesulphonyl chloride and pyridine, cyclised smoothly to give the oxide (**14**) further supporting the relative disposition of the C-6 hydroxyl and the C-7 isopropyl residue bearing the primary alcoholic group being *cis*.

Structure and stereochemistry of **3**

The lactone (**3**), a white crystalline solid, was obtained as a minor constituent. It exhibited IR bands at 3400, 1760, 1460, 1170 and 960 cm^{-1} due to saturated γ-lactone and hydroxyl group. Its UV spectrum exhibited an absorption maximum at 211 nm (ε 8658). The IR, UV, PMR spectra of **3** were very similar to the dihydro derivative (**4**) of lactone (**1**). Thus, by analogy, in the PMR of **3**, the singlets at 1.08 and 1.80 were ascribed to C-10 and C-4 methyls, respectively, the doublet at 1.3 ($J=3$ Hz) to C-11 secondary methyl, the singlet at 5.1 to C-6 proton and the quartet at 2.46 ($J=2.8$ Hz) to C-11 proton. Hence, **3** was an eudesmanolide similar to **1** and **2**.

On reduction (LAH/THF) **3** gave a triol (**15**) which on acetylation (Ac_2O/Py) gave a complex mixture, from which the diacetate (**16**) was isolated and characterized. Compound (**16**) exhibited in its IR band at 3425 cm^{-1} due to hydroxy group. In its PMR spectrum the C-6 proton, which was shifted downfield, appeared at 5.7, while methylene protons at C-12 appeared as doublets at 4.4 and 4.0, due to vicinal and geminal couplings. The downfield shifts for the C-12 and C-6 protons were attributed as due to the acetate formation. A highfield doublet at 1.05 ($J=3$ Hz) was due to C-11 methyl group. The singlets due to the C-4

and C-10 methyl were also shifted downfield and appeared at 2.07 and 1.17 respectively.

The lactone (**3**) yielded a ring-cleaved lactone (**17**) on ozonolysis, which exhibited in its IR bands at 1775 and 1708 cm^{-1} due to lactone group and a keto group on a cyclohexane ring respectively. Since the IR band absorption due to aldehyde function was absent and the PMR spectrum did not show any signal due to aldehydic proton, it was concluded that the ring cleaved lactone was the diketo lactone (**17**). This supported the basic eudesmenic skeleton for **3**.

The $C_{11}-CH_3$ signal at 1.3 in **3** was solvent dependent and appeared at 1.13 in benzene as solvent. Thus an upfield shift of 0.17 ppm in benzene[16] indicated the stereochemistry of the C-11 methyl group as pseudo-equatorial. The signals due to C-6 proton in **3** and its derivatives were closely similar to those of **1** and **2** and their derivatives. Therefore, it was concluded that the stereochemistry of the C-6 proton was also α in **3**.

The stereochemistry of the C-7 hydroxy group was concluded to be β, since **3** did not show any OH-π interaction in its IR spectrum (0.5 *M*, 5 cm cell, dil soln in CCl_4).

The triol (**15**) obtained by reduction of **3** with LAH/THF, underwent cyclisation, though not facile, to give **18** on treatment with *p*-toluenesulphonyl chloride and pyridine. This observation indicated that the C-6 hydroxyl and the C-7 isopropyl residue bearing the hydroxyl group were *trans* to each other. Thus, lactone (**3**) is a dihydro derivative of lactone (**1**), different from **4** obtained by hydrogenation of **1**. Since on the basis of PMR spectral analysis, lactone (**3**) is shown to possess a pseudo-equatorial methyl group, the synthetic **4** should possess a pseudo-axial C-11 methyl group.

Experimental Procedure*

Extraction of the flower tops of Sphaeranthus indicus

The powdered flower tops obtained from the air-dried plant material (20 kg) were extracted three times with hexane (50 litres × 3) in a mechanically stirred extractor, on each occasion for 6 hr at room temperature. The extract was allowed to stand overnight, collected, filtered and combined. The solvent was removed at 40±2°C (bath) *in vacuo*, to yield a greenish yellow, viscous oil (688 g, 4.7% by weight of the dried flower tops): acid val: 17.12; sap. value: 55.04.

The residue (19.3 kg) was extracted with chloroform (50 litres) at room temperature and worked-up in the same way as described for the hexane extract to yield a dark green, viscous oil (400 g, 2% by weight of the dried flower tops).

Separation of constituents of the chloroform extractive

The chloroform extractive (200 g) was chromatographed on silica gel (3.0 kg, 1:15) and eluted with hexane (15 litres), hexane-ethyl acetate of varying proportions (88:12, 40 litres), (75:25, 30 litres); and (50:50, 32 litres) and methanol (15 litres) to yield five fractions: A1 (5.0 g), A2 (35 g), A3 (30 g), A4 (38 g), A5 (92 g). On the basis of TLC analysis, fraction A3 (30 g) was further chromatographed over silica gel (1:7, 200 g) and eluted with hexane (1 litre), hexane-ethyl acetate (95:5, 2.5 litres; and 90:10, 12 litres) and methanol (2.5 litres) to give fractions B_1 (0.0 g), B_2 (5.0 g), B_3 (10.0 g), B_4 (15.0 g).

Fraction B_3 (10 g), being essentially a lactone mixture, was dissolved in ethanol (50 ml) and treated with morpholine (7 ml) at the room temperature and the mixture left at 0° for 16 hr, when **1** and **2** formed Michael adducts with morpholine and **3** did not. Chromatography of this mixture (12.7 g) over silica gel (200 g, 1:16) yielded the saturated γ-lactone (**3**, 1.7 g) on elution with hexane-ethyl acetate (85:15, 41 litres) and the Michael adducts of **2** (2.9 g) and **1** (8.1 g) on elution with hexane-ethyl acetate (80:20, 2.8 litres) and (70:30, 4.2 litres) respectively. Crystallisation from ethyl acetate-hexane yielded the adduct of **1** (8 g), m.p. 140-42° as shining needles and that of **2** (2.7 g) as white crystals, m.p. 153-55°. The lactones were regenerated from their adducts by the following procedure.

The adducts (1 g) were separately stirred with methyl iodide (1.5 ml) at room temperature for 3 hr, treated with aq $NaHCO_3$ (5%, 50 ml) and left overnight. The reaction mixtures were diluted with water, extracted with chloroform and worked up as usual to give the respective lactones which were recrystallised from pentane-ethyl acetate of yield **1** (6.0 g), **2** (2.0 g) and **3** (1.7 g).

Properties of **1**

A white crystalline solid, m.p. 72-73°, $[\alpha]_D^{23}-63.16°$ (*c*, 3.07); IR: 3625, 3450, 3250, 1875, 1760, 1625, 1450, 1425, 1375, 1260, 1225, 1175, 1150, 1135, 1000, 970, 940, 850, 800 and 750 cm^{-1} (Found: C, 72.3; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.6; H, 8.1%); mass: *m/z* 248 (M^+), 233, 215, 187, 178, 169, 109, 107, 105, 95, 93, 91, 79, 77, 67, 55, 53, 43, **41** and 39.

Dihydro derivative (**4**) *from* **1**

The lactone (**1**, 300 mg), in ethanol (30 ml) containing PtO_2 (35 mg) was stirred under H_2 atmosphere. After absorption corresponding to 1 mol

*Standard analytical practices and standard instruments manufactured by reputed houses were used for all measurements.

was over, the product was filtered and the solvent removed *in vacuo*. The residue on crystallisation from ethyl acetate-hexane yielded fine, white crystals of **4** (300 mg), m.p. 97-99°, $[\alpha]_D^{23}$ −13.07°; IR: 3425, 1765, 1640, 1450, 1375, 1260, 1230, 1170, 1125, 1120, 1075, 980, 960 and 750 cm^{-1} (Found: C, 72.1; H, 8.8. $C_{15}H_{22}O_3$ requires C, 72; H, 8.8%); mass: *m/z* 250 (M^+), 235, 217, 189, 161 and 60.

Dehydration of **4**: *Isolation of triene lactone* (**5**)

To a solution of **4** (200 mg) in pyridine (3 ml) was added $POCl_3$ (2 ml) at 0°C with stirring. After stirring for 8 hr the reaction mixture was diluted with ice-cold water and extracted with chloroform. Removal of the solvent *in vacuo* furnished a residue which was chromatographed over silica gel (1:25, 5.0 g) and eluted with hexane, hexane-ethyl acetate (95:5) and ethyl acetate. The hexane-ethyl acetate (95:5) fraction after removal of solvent and cooling deposited yellow crystals of **5** (60 mg) which recrystallised from hexane in yellow plates, m.p. 124-26°, $[\alpha]_D^{20}$ −348.5° (*c*, 0.12); IR (CS_2): 3000, 2980, 2920, 2850, 1780, 1755, 1640, 1615, 1350, 1330, 1320, 1275, 1225, 1110, 1095, 1075, 1015, 995, 940 and 750 cm^{-1}; UV: 330 nm (ε 20093) (Found: C, 78.3; H, 7. $C_{15}H_{18}O_2$ requires C, 78.2; H, 7.9%); mass: *m/z*, 230 (M^+), 215, 187, 105, 91, 53 and 39.

Monoepoxide (**8**) *from* **1**

To a soln of **1** (300 mg) in chloroform (30 ml) was added perbenzoic acid (1 mol) in chloroform at −5° and the reaction mixture kept at 0° for 24 hr. The reaction mixture was washed successively with aq $NaHSO_3$ (5%), $NaHCO_3$ (5%), and water and dried. The residue obtained after removal of solvent *in vacuo*, on cooling, gave white crystals of **8** (310 mg), which recrystallised from ethyl acetate-hexane, m.p. 168-70°, $[\alpha]_D^{23}$ −41.44° (*c*, 2.66); IR 3410, 1760, 1260, 1130, 1000, 950, 900 and 800 cm^{-1}; UV: 214 nm (ε 6759) (Found: C, 67.8; H, 7.2. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.5%); mass: *m/z* 264 (M^+), 249, 221, 188, 135, 55, 53, 43 and 41.

LAH reduction of **4**: *Formation of triol* (**9**)

A soln of **4** (800 mg) in dry THF (25 ml) was added gradually (40 min) under dry conditions to a suspension of LAH (600 mg) in dry THF (20 ml) at 90°, under reflux, with stirring. After additional stirring for 2 hr at 90°, the reaction mixture was cooled and moist ethyl acetate was added water slowly till excess LAH was destroyed. To this was added slowly and extracted with chloroform usual work-up yielded the crude **9** as a syrupy liquid, was purified by chromatography on silica gel (8.0 g), using hexane-ethyl acetate (90:10) as the eluent and recrystallised from ethyl acetate-hexane, m.p. 152-54°, $[\alpha]_D^{23}$ +1.35° (*c*, 4.87) (Found: C, 70.6; H, 10.1. $C_{15}H_{26}O_3$ requires C, 70.9; H, 10.3%); mass: *m/z* 254 (M^+), 203, 137, 130, 129, 116, 95, 93, 79, 57, 55, 43, 32, 28.

Cyclisation of **9**: *Formation of oxide* (**10**)

To a soln of **9** (138 mg) in dry pyridine (4.9 ml) was added with stirring *p*-toluenesulphonyl chloride (72 mg) and heated under dry conditions on a water-bath with stirring for 24 hr. The reaction mixture was cooled and ethyl acetate (1 ml) added, followed by 5% aq. $NaHCO_3$ (1 ml). The mixture was stirred for 5 min and diluted with 5% aq $NaHCO_3$ and ethyl acetate. The aqueous layer was extracted with chloroform and the combined organic layer was dried, concentrated *in vacuo* (bath temp. 20-25°) and the last traces of pyridine were removed by co-distillation with benzene. The residue after chilling, solidified to give **10** (100 mg), which crystallised from ethyl acetate, m.p. 134-36° (Found: C, 76.0; H, 9.9. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.2%); mass: *m/z* 236 (M^+), 222, 203, 147, 109, 107, 55, 53, 43, 41 and 28.

Properties of lactone (**2**)

A white crystalline solid, m.p. 62-63°, $[\alpha]_D^{23}$ −44.21° (*c*, 2.09); IR: 3640, 3475, 2930, 1875, 1760, 1650, 1440, 1360, 1340, 1275, 1260, 1220, 1175, 1135, 1070, 960, 940 and 800 cm^{-1} (Found: C, 72.7; H, 8.0. $C_{15}H_{20}O_3$ requires C, 72.6; H, 8%); mass: *m/z* 248 (M^+), 233, 215, 187, 178, 169, 109, 105, 79, 67, 55, 41 and 40.

Monoepoxide (**11**)

The monoepoxide (**11**) was prepared from **2** by the same procedure as employed for the monoepoxide (**8**) from **1**, $[\alpha]_D^{23}$ −17.44° (*c*, 1.29); PMR: δ 1.12 (3H, *s*, $C_{11}-CH_3$) 1.36 (3H, *s*, $C_{11}-CH_3$), 3.94 (1H, *s*, C_6-H), 5.88 and 6.14 (1H each, *s* each, $C_{13}-CH_2$).

Dihydro derivative (**12**) of lactone (**2**)

It was prepared by catalytic hydrogenation of **2**, employing the same procedure as described for **4**; white crystalline solid, m.p. 129-31°, $[\alpha]_D^{23}$ −14.62° (*c*, 2.83) (Found: C, 72.1; H, 8.6. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.8%).

LAH reduction of **12**: *Formation of triol* (**13**)

Compound (**12**) was reduced by the same procedure described for (**9**); white crystalline solid, m.p. 147-49°, $[\alpha]_D^{23}$ +27.25°; IR: 3560 and 3400 cm^{-1}, PMR: δ 1.26 (3H, *s*, $C_{10}-CH_3$), 1.80 (3H, *s*, $C_{11}-CH_3$), 1.56 (3H, *d*, $C_{13}-CH_3$), 3.7, and 4.16 (1H each, double doublets, J_{AB} = 2.0 Hz, J_{BC} = 5.5 Hz, C_{12} − protons), 4.63 (1H, *s* C_6-H) (Found: C, 70.7; H, 10.4. $C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3%).

Cyclisation of **13**: *Formation of oxide* (**14**)

Cyclisation of **13** was effected in the manner described for **10**. In this case, the reaction mixture was heated on a water-bath for 5 hr for the completion of the reaction; white crystalline solid, m.p. 134-36°; IR: 3400 cm^{-1}; PMR: δ 0.95 (3H, *d*, *J* = 3 Hz, $C_{11}-CH_3$),

1.08), 3H, *s*, $C_{10}-CH_3$), 1.68 (3H, *s*, $C_{11}-CH_3$), 4.28 (1H, *s*, C_6-H); mass: *m/z* 236 (M^+), 222, 203, 147, 109, 107, 55, 43, 41, 28.

Properties of the lactone (**3**)

White crystalline solid from ethyl acetate-hexane, m.p. 81-82°, $[\alpha]_D^{23}-61.80°$; IR: 3400, 2920, 1760, 1650, 1460, 1375, 1350, 1300, 1240, 1225, 1200, 1175, 1150, 1125, 1080, 1040, 980, 960, 910, 880, 860, 840, 800 and 740 cm^{-1}; IR (0.5 *M*, 5 cm cell, dil soln in CCl_4) 3590 cm^{-1}; UV: 211 nm (ε 8658) (Found: C, 72.0; H, 8.7. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.8%); mass: *m/z* 250 (M^+), 235, 189, 161 and 60.

LAH reduction of **3**: *Formation of triol* (**15**)

Triol (**15**) was prepared by reduction of **3** using LAH/THF as before; $[\alpha]_D^{23}+37.43°$ (c, 6.0); IR: 3475 cm^{-1}; PMR: δ 1.1 (3H, *d*, $J=2.5$ Hz, $C_{11}-CH_3$), 1.25 (3H, *s*, $C_{10}-CH_3$), 1.8 (3H, *s*, $C_{11}-CH_3$), 3.7 and 3.94 (1H each, double doublets, $J_{AB}=1.5$ Hz, 1.0 Hz and $J_{BC}=4.0$ Hz, 4.0 Hz, C_{12}-protons), 4.68 (1H, *s*, C_6-H) (Found: C, 70.6; H, 10.4. $C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3%).

Diacetate (**16**)

The triol (**15**, 100 mg) was treated with a mixture of acetic anhydride (2 ml) and pyridine (3 ml) and kept at the room temperature overnight. The product was worked-up to furnish a mixture of compounds, which was chromatographed on silica gel (1:25, 2.5 g) and eluted with hexane-ethyl acetate (99:1) to yield **16** (55 mg); IR: 3425, 2910, 1730, 1450, 1370, 1230, 1175, 1130, 1020, 960 and 850 cm^{-1}.

Ozonisation of **3**: *Formation of ring-cleaved lactone* (**17**)

A stream of ozonised oxygen was passed through a soln of **3** (300 mg) in chloroform (30 ml) at −70° (till a soln of KI was turned orange). The ozonide was decomposed with Zn dust and acetic acid by stirring it overnight. The product was filtered and worked-up to yield the diketolactone (**17**, 200 mg), $[\alpha]_D^{23}-50.01°$; IR: 3440, 2920, 1775, 1708, 1460, 1400, 1375, 1245, 1170, 1090, 1030, 950, 900, 850, and 750 cm^{-1}; PMR: δ 1.08 and 2.14, (3H each, *s*, $C_{10}-$ and $C_{11}-CH_3$), 5.18 (1H, *s*, C_6-H). The C-6 proton signal was shifted downfield (5.18) from its normal position (5.10) due to the electronegative centre at C-5 (Found: C, 64.0; H, 7.6. $C_{15}H_{22}O_5$ requires C, 76.2; H, 7.9%); mass: *m/z* 282 (M^+), 69, 56, 32 and 28.

Cyclisation of triol (**15**): *Formation of oxide* (**18**)

The oxide (**18**) was prepared from **15** following the same procedure as before but heating on a water-bath for 24 hr. Due to paucity of material it could not be processed as carefully as before but could be otherwise characterised; PMR: δ 1.15 (3H, *s*, $C_{10}-CH_3$), 1.74 (3H, *s*, $C_{11}-CH_3$), 4.28 (1H, *s*, C_6-H) (Found: C, 76.1; H, 10.6. $C_{15}H_{24}O_2$ requires C, 76.2; H, 10.2%).

Monoepoxide (**19**)

It was prepared from **3** following the procedure adopted earlier; PMR: δ 1.12 (3H, *s*, $C_{10}-CH_3$), 1.23 (3H, *d*, $J=2$Hz, $C_{11}-CH_3$), 1.40 (3H, *s*, C_4-CH_3), 2.5 (1H, *q*, $J=4$Hz, $C_{11}-H$), 4.02 (1H, *s*, C_6-H).

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Hydroperoxyclerodane—A Novel Diterpene from *Solidago altissima* Linn.

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The novel diterpene hydroperoxyclerodane, isolated from the roots of *Salidago altissima* Linn., has been characterized as methyl 3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenoate (I) on the basis of spectroscopic evidences. Several other known clerodane derivatives have also been isolated and their identities established either by direct comparison with authentic samples or by rigorous spin decoupling experiments.

In pursuing our interest[1,2] in the diterpene constituents of the Compositae we have chemically reexamined the plant *Solidago altissima* Linn. (subtribe: Asterae). Previous work on this plant led to the isolation of a number of *trans*-clerodane diterpenes[3-5]. Later on their stereochemistry was revised by Yamamura *et al.*[6] from chemical studies and biogenetic point of view leading to conclusion that clerodanes having oxygen function at C-6 belonged to the *cis*-clerodane group and those having no oxygen function at C-6 belonged to the *trans*-clerodane series. In the *cis*-series the configuration was 9β-methyl and 10α-H, while in the *trans*-series it was 10β-H and 9α-methyl. The cooccurrence of *cis*- and *trans*-clerodanes in this species is remarkable.

During reinvestigation of the roots of *S. altissima* we have isolated a novel diterpene, hydroperoxyclerodane, which has been assigned the structure as methyl 3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenoate (I), alongwith methyl esters of kolavenic acid[7] (IIa), 2-oxokolavenic acid[8] (IIb), 7α-acetoxykolavenic acid[4] (IIc), solidagolactone VII[3,9] (IIIa) and corresponding tiglate[10] (IIIb), solidagolactone-V[4] (IV), II[4] (Va), III[4] (Vb), methyl 6β-angeloyloxy-(VIa)- and 6β-tigloyloxy- *cis*-kolavenoates[5] (VIb), methyl ester of solidagonal acid[1] (VII) and 16-hydroxy-2-oxokolavenic-15-oicacid lactone[1] (VIII).

The structure of the hydroperoxyclerodane as I was deduced from extensive spin decoupling experiments. The presence of the hydroperoxide group was indicated by the characteristic lowfield signal at δ8.0 in the high resolution (400 MHz) PMR spectrum (Fig. 1). This was further supported by the appearance of a peak at 3520 cm^{-1} in the IR spectrum. Further the presence of hydroperoxyl group was confirmed by its reduction to the alcohol (IX) by treating its methanolic solution with triphenylphosphine for 1 hr at room temperature. The position of the hydroperoxide group followed from the broadened double doublet at δ4.60 due to H-3 proton which showed coupling with the vinylic protons. The olefinic H-14 proton appeared as a triplet quartet at 5.63 while vinylic (exomethylene) protons H-18 and H-18′ appeared as a pair of broad singlets at 4.85 and 4.75 respectively. The signals at 1.97 and 1.83 (pair of *ddd*) were due to H-12 and H-12′ protons while the multiplets at 1.55 and 1.40 were due to H-10 and H-11 protons respectively. Singlets at 1.05 and 0.72 were assigned to H-19 and H-20 methyl protons and a pair of doublets at 2.15 and 0.80 were due to H-16 and H-17 methyl protons respectively. The carbomethoxy protons appeared as a sharp singlet at 3.67. The sequence of protons were established by spin decoupling. These data were comparable with those of corresponding compounds of *trans*-kolavenate series.

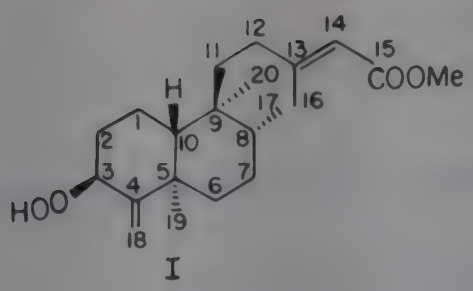
In its mass spectrum the parent ion peak was very weak. Even the chemical ionisation mass spectrometry did not prove to be very useful. However, an abundant ion peak at *m/z* 332 was attributed to $[M-H_2O]^+$ corresponding to the fragment $C_{21}H_{32}O_3$ as confirmed by its appearance in the high resolution spectrum at *m/z* 332, 235. The other important fragments were at *m/z* 317 $[M-OOH]^+$, 301 [332-OMe]$^+$, 300 [332-MeOH]$^+$, 285 [300-Me]$^+$, 183 $[C_{14}H_{21}]^+$ 95 etc.

This compound seems to arise from the kolavenic acid by an ene reaction (Scheme 1). Based on these data the hydroperoxyclerodane can be assigned the structure as methyl 3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenoate (I).

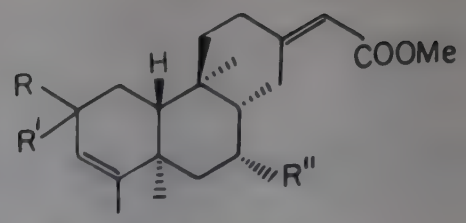
The identity of the known compounds were established by direct comparison with authentic samples or by rigorous spin decoupling of their PMR spectra.

Experimental Procedure

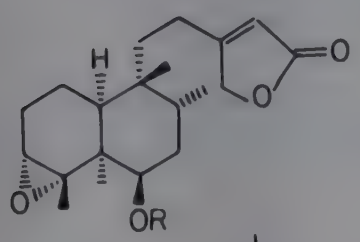
The IR spectra (ν_{max} in cm^{-1}) were recorded in $CCl_4/CHCl_3$ on a Perkin-Elmer model 137 E and PMR spectra in $CDCl_3$ on a Bruker WM 400



I



IIa, R = R' = R'' = H,
IIb, R = R' = O, R'' = H,
IIc, R = R' = H' R'' = OAc



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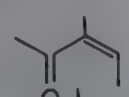

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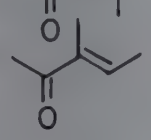

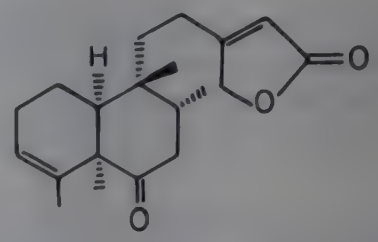

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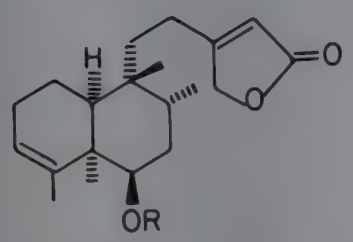

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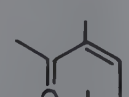

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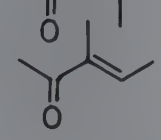
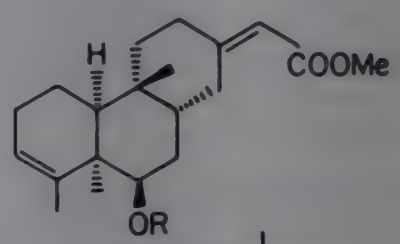
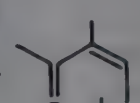
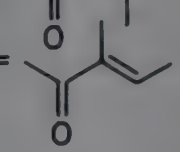


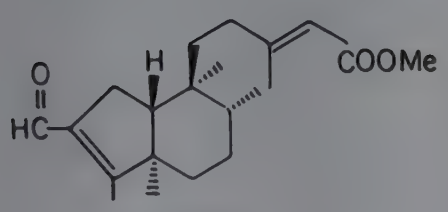


VIa, R =



VIb, R =





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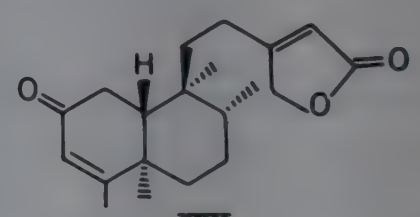
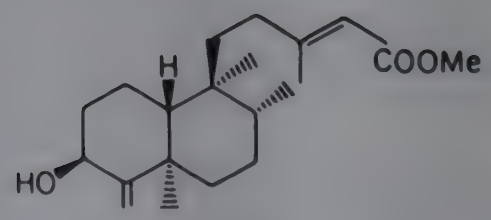
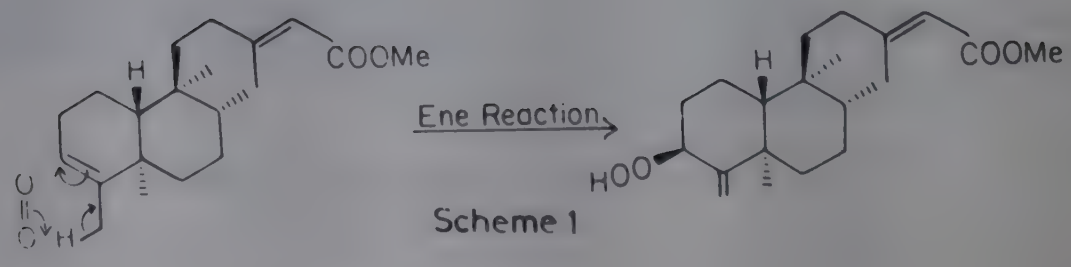


VIII



IX



Scheme 1

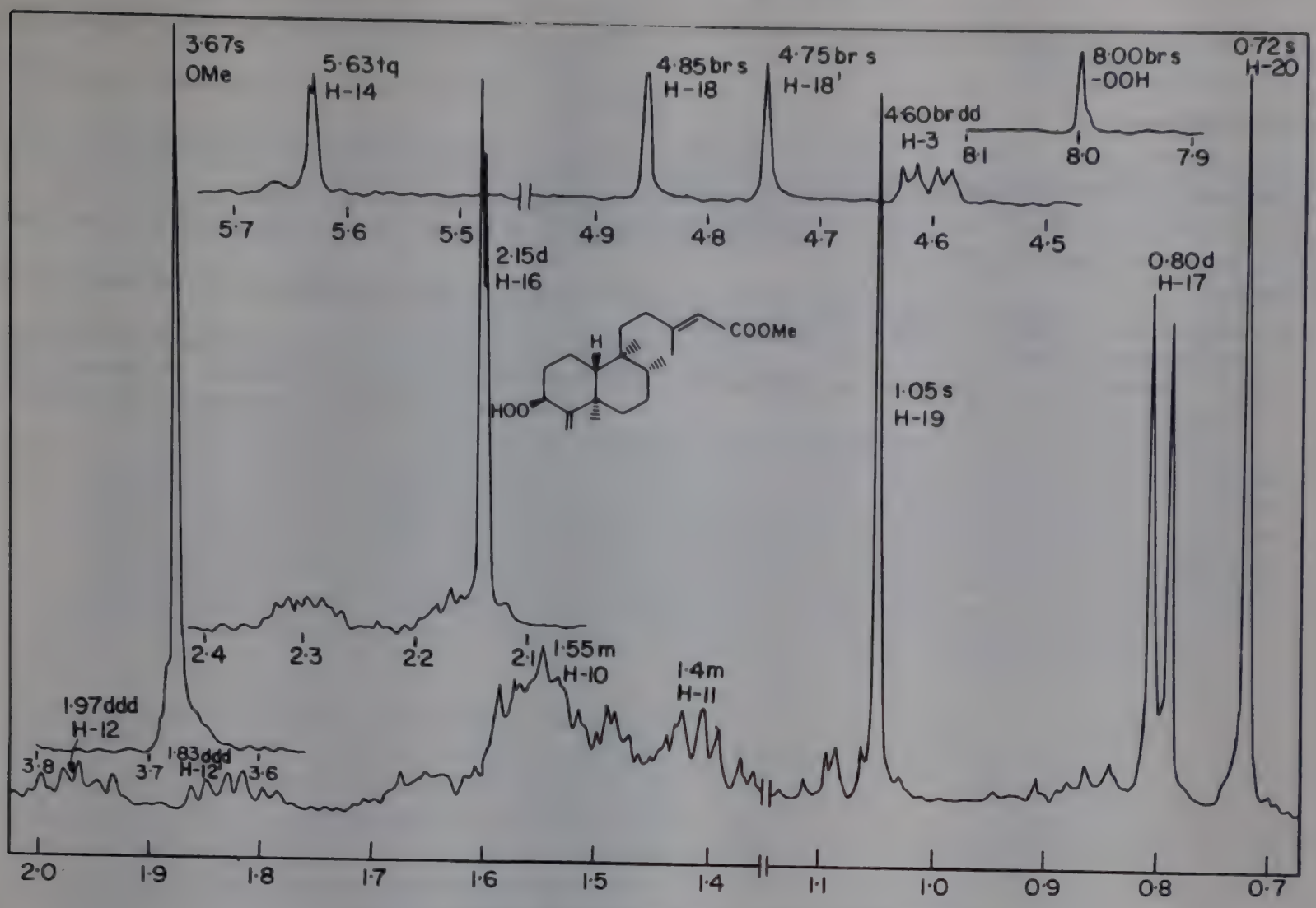


Fig. 1—^{1}H NMR (400 MHz) spectrum of methyl 3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenoate

(400 MHz) instrument; chemical shifts are reported in (δ-scale) downfield from internal TMS. Mass spectra were recorded on a Varian MAT 711 at 70 eV.

Isolation

The air-dried roots (1.5 kg), collected from Jaipur, were extracted with cold petroleum ether-ether (2:1) for 24 hr. Concentrated extract was column chromatographed over silica gel and the following fractions were collected: Fraction-1 (petrol); fraction-2 (petrol-ether, 4:1); fraction-3 (petrol-ether, 1:1) and fraction-4 (ether). Fraction-2 afforded kolavenic acid (150 mg). TLC (aluminium sheets 0.1 mm, SiO_2 PF 254, detection by UV light and by spraying with $KMnO_4$ solution) of fraction-3 using ether-petrol (2:3), after addition of diazomethane gave methyl 6β-angeloyloxykolavenoate (15 mg, R_f, 0.7) and methyl 6β-tigloyloxy-*cis*-kolavenoate (20 mg, R_f 0.6), methyl 7α-acetoxykolavenoate (20 mg, R_f 0.5), methyl 2-oxokolavenoate (15 mg, R_f 0.4) and the new hydroperoxyclerodane (15 mg, R_f 0.3). Fraction-4 on repeated TLC using CH_2Cl_2-benzene-ether (4:4:1, several developments) gave solidagonal acid (5 mg, R_f 0.7), solidagolactone-VII (10 mg, R_f 0.6) and its corresponding tiglate (12 mg, R_f 0.5), solidagolactones-II (10 mg), III (10 mg) and V (10 mg) (R_f 0.4, 0.35, 0.30 respectively) and 16-hydroxy-2-oxokolavenic-15-oicacid lactone (20 mg, R_f 0.15).

Methyl 3β-hydroperoxy-4,18-dehydro-3,4-dihydrokolavenoate (I)

It was obtained as a colourless oil; IR (CCl_4): 3520 (−OOH), 1715 (C=CCO$_2$R), 1645 (C=C) cm^{-1}; PMR ($CDCl_3$): 4.60 (*bdd*, H-3), 1.55 (*m*, H-10), 1.40 (*m*, H-11), 1.97 (*ddd*, H-12), 1.83 (*ddd*, H-12′), 5.63 (*tq*, H-14), 2.15 (*d*, H-16), 0.80 (*d*, H-17), 4.85 (*bs*, H-18), 4.75 (*bs*, H-18′), 1.05 (*s*, H-19), 0.72 (*s*, H-20), 3.67 (*s*, COOMe), 8.00 (*s*, −OOH). Missing signals are complex multiplets. [*J*: 8, 17 = 7; 11, 12 = 13; 11, 12′ = 6; 11′, 12 = 5.5; 11′, 12′ = 12; 12, 14 = 14; 16 = 1; 12, 12′ = 13 Hz]; MS (rel. int.): *m/z* 332.235 [M−H$_2$O]$^+$ (5) (calc. for $C_{21}H_{32}O_3$: 332.235) 317 [M−OOH]$^+$ (28), 301 [332−OMe]$^+$ (9), 300 [332-MeOH]$^+$ (6), 285 [300-Me]$^+$ (12), 189 [$C_{14}H_{21}$]$^+$ (42), 95 (84), 55 (100).

Reduction of I to the alcohol (IX)

A solution of I (10 mg) in MeOH was treated with triphenylphosphine (10 mg) for 1 hr at room temperature. The solvent was evaporated to dryness and the residue purified by preparative TLC (CH_2Cl_2 −C_6H_6−Et_2O, 4:4:1) to yield IX (7 mg) as a colourless oil, PMR spectrum of IX was similar to that of I except the signal at δ 8.00 was missing with slight

upfield shift of H-3 proton;MS (rel. int.): m/z 334 $[M^+]$ (6), 316 $[M-H_2O]^+$ (20).

Acknowledgement

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Reaction of Some Longibornane-based γ-Bromoketones with Sodium-Potassium Alloy†

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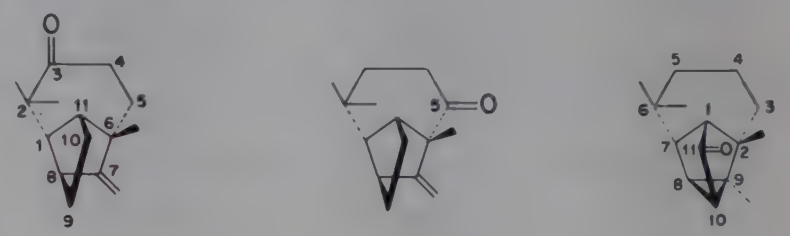
While 5-ketolongifolene (**2**)/11-ketolongicyclene (**3**) undergo Wagner-Meerwein rearrangement to give the expected 3-keto-8-bromolongibornane (**5**)/11-keto-8-bromolongibornane (**6**) on exposure to HBr-AcOH, 3-ketolongifolene (**1**) fails to give the expected 5-keto-8-bromolongibornane (**4**) but generates, instead, the transannular tetracyclic dibromide (**7**). The acetate **9** (derived from 3β-alcohol **8** obtained by LAH reduction of **1**) on treatment with HBr-AcOH, followed by hydrolysis and oxidation, however, affords **4**. When these three γ-bromoketones (**4**, **5** and **6**) are exposed to sodium-potassium alloy in ether, only **5** suffers the expected fragmentation to give the bicyclic keto-olefin **18** (plus **19**); only reductive debromination takes place in the case of the other two: **4**→**15** and **6**→**17**. The bromodiketone (**13**) on reaction with the alloy gives a complex mixture from which only one pure compound could be isolated and characterized as the fragmented vinylidenedione **21** (15%).

Our interest in the synthesis of β-santalene[1] and other bicyclic sesquiterpenes from bridged tricyclic longifolene derivatives prompted us to prepare some longibornane-based γ-bromoketones and study the action of sodium-potassium alloy on these substrates for achieving olefin-forming ring fragmentation[2].

The ready accessibility of 3-ketolongifolene[3] (**1**)/5-ketolongifolene[3] (**2**) and 11-ketolongicyclene[4] (**3**) suggested the addition of hydrogen bromide to these substrates for delivering the γ-bromoketones **4**/**5** and **6** respectively via a Wagner-Meerwin rearrangement. While **2** and **3** gave the expected **5** and **6** respectively, the product in case of **1** was a novel dibromide (**7**)[5] obtained via a transannular cyclization (Scheme 1) between the proximal C-3 and C-7. 5-Keto-8-bromolongibornane (**4**) was, however, generated in an indirect manners as follows: 3β-acetoxylongifolene (**9**) (from **8** via LAH reduction of **1**) on exposure to HBr-AcOH gave **10** (R = Ac) which on hydrolysis/oxidation afforded **4** without any difficulty. The fourth substrate selected for the study was a bromo-1,2-diketone of the type **13** in which the bromine was on the γ-carbon with respect to one of the keto groups. It has been reported[6] that **13** is formed in an abnormal Jones' oxidation of the bromoalcohol (**11**). Several optimization experiments were attempted before we could achieve an efficient and cheap method for generating **11** from ω-bromolongifolene[7] by hydration. Thus the targeted alcohol (**11**) was obtained in a decent yield (65%) using trifluoroacetic acid (TFA) in nearly one-fourth of the reported amount[6a]; in our large-scale work this improvement was highly significant. Oxidation of **11** with a large excess of Jones' reagent for a prolonged



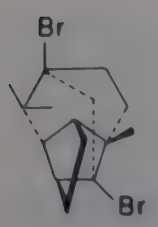
SCHEME 1

period gave the major bromodiketone (**13**) (42%) plus the minor bromomonoketone (**12**) (6%) in the neutral part, along with a new lactone acid‡.

Olefin-forming ring fragmentation of the γ-bromoketones **4**/**5**/**6** and of **13** was studied in

†NCL Communication No. 3859

‡Assignment of structure and mechanism of its formation will be discussed elsewhere.



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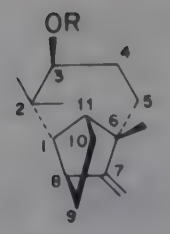

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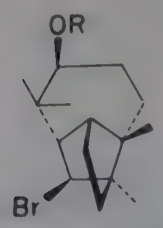
9 : R = Ac



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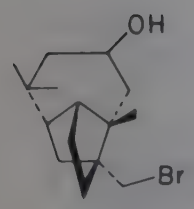

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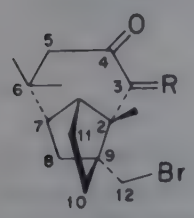
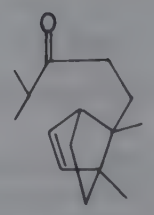


12 : R = H, H

13 : R = O



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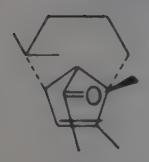

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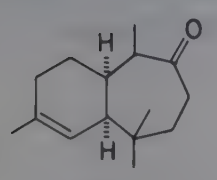

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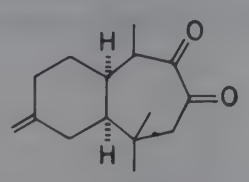

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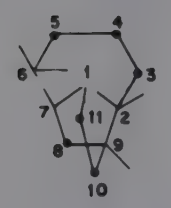

20

anhydrous ether using liquid sodium-potassium alloy[8]; the crude product was oxidised with Jones' reagent (so that any alcohol also formed by ketone reduction in the alloy reaction was reconverted to the carbonyl compound) before distillation. In the case of **4/6**, this reaction failed to give the expected fragmented products **14/16** but afforded the reductively debrominated compounds **15/17** as the only products. On the other hand, the product-outcome in the case of **5** was a binary mixture consisting of the ring-fragmented bicyclic keto-olefin (**18**) (35%) and the bromine-free ketone (**19**) (34%) which were separated on a column of 15% $AgNO_3$-silica gel; **18** is a useful synthon which has been transformed[9] into γ-himachalene—a naturally occurring sesquiterpene of *Cedrus atlantica*. It must however be mentioned here that the sodium-potassium alloy reaction on **4/5/6** has effectively given 5-ketolongibornane (**15**)/3-ketolongibornane (**19**)/11-ketolongibornane (**17**) thus providing the three missing ketolongibornanes out of the possible six, (see **20**: the other known three being 4-keto-, 8-keto- and 10-keto-longibornanes). From the

Table 1—Diagnostic Spectral Data (IR/PMR) of all Six Possible Ketolongibornanes

No.	Longibornane (**20**)	IR (ν, cm^{-1}) C=O	IR (ν, cm^{-1}) $-CH_2-CO-$	PMR (δ, tertiary Me singlets only)
1.	3-Keto	1695	1435	1.08, 1.02, 0.90, 0.77
2.	4-Keto[10]	1700	1420	1.03, 0.88, 0.88, 0.85
3.	5-Keto*	1690*, 1730	1435	1.06, 0.90, 0.86, 0.83
4.	8-Keto[11]	1740	—	1.14, 1.00, 0.91, 0.91
5.	10-Keto[12]	1740	1420	1.08, 1.00, 0.92, 0.88
6.	11-Keto[13]	1740	1420	1.05, 1.05, 0.90, 0.83

*Splitting due to Fermi resonance

diagnostic point of view the spectral data (IR/PMR) of the six, closely related, longibornane-based ketones assume importance and hence they have been gathered in Table 1.

When the bromodiketone (**13**) was exposed to sodium-potassium alloy in ether as described earlier, a complex mixture was formed unlike in the case of bromoketones **4/5/6**. On chromatography over silica gel only one pure compound, $C_{15}H_{22}O_2$ (M^+ 234), could be isolated and was characterized as the expected himachalane-based olefinic diketone† **21** (15% yield). It may also be mentioned here that when **13** was refluxed with zinc in dioxane (or DMF) for several hours, there was no evidence of any fragmented vinylidene diketone in the resulting complex reaction mixture.

Experimental Procedure

Light petroleum refers to fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4. Melting and boiling points are uncorrected: m.ps were taken in capillaries on a Electrothermal melting point apparatus; b.ps refer to bath temp. in those cases where short path bulb-to-bulb distillations were carried out. $AgNO_3$-silica gel was prepared by the method[14] of Gupta and Sukh Dev. IR spectra (ν_{max} in cm^{-1}) were recorded as smears (liquid) or nujol mulls (solid) on a Pye-Unicam SP-3 IR spectrophotometer. PMR spectra were obtained on Varian T60/FT 80A/Bruker WH-90 spectrometers and mass spectra on a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system.

3-Ketolongifolene (**1**) and 5-ketolongifolene (**2**) were prepared via the LTA rection sequence on longifolol as described by Jadhav and Nayak[3].

†This compound is highly air-sensitive and a satisfactory elemental analysis could not be obtained.

11-Ketolongicyclene (**3**) was prepared by hydration/oxidation of dehydrolongifolene as reported[4].

HBr addition to 5-*ketolongifolene* (**2**): *Formation of* 3-*keto*-8-*bromolongibornane* (**5**)

A mixture of **2** (2.0 g) and 32% HBr-AcOH (20 ml) was kept at room temperature for 18 hr, poured into water (100 ml), extracted with ether, the ether extract washed with 5% aq Na_2CO_3, brine, dried, sovent removed and the residue recrystallized from methanol to furnish colourless crystals of **5**, m.p. 122-23° (1.95 g); IR(nujol): 1700, 915, 890, 785, 730; PMR(CCl_4): δ 3.97, (*dd*, 1H, $-\overset{|}{C}HBr$); 1.30, 1.27, 1.13, 0.83 (four tertiary Me singlets); Mass: *m/z* 298, 300 (M^+). (Found: C, 60.7; H, 7.9; Br, 26.7. $C_{15}H_{25}OBr$ requires C, 60.2; H, 7.7. Br, 26.3%).

Action of HBr on 3-*ketolongifolene* (**1**): *Formation of adamantoid dibromide* (**7**)

A mixture of **1** (0.8 g) and 32% HBr-AcOH (10 ml) was kept at room temperature for 18 hr. The mixture was poured into water, extracted with ether, washed with 5% aq. Na_2CO_3, brine, dried, solvent removed and the residue chromatographed on silica gel/IIa (30 g; 40 cm × 1.5 cm): Fr. 1, light petroleum-benzene (1:1), 4 × 50 ml, pure; and Fr. 2, benzene, 2 × 50 ml, mixture (0.25 g).

Fr. 1, which solidified was recrystallized from methanol to yield colourless needles of **7**, m.p. 139-40° (0.55 g); IR(nujol): 955, 890, 860; PMR(CCl_4): δ 2.97 (*s*, 2H, $Br-\overset{|}{C}-CH_2-\overset{|}{C}-Br$); 1.32, 1.17, 1.08 (three tertiary Me singlets); Mass: *m/z* 281, 283 ($M^+ - Br$). (Found: C, 50.2; H, 6.3; Br, 43.6. $C_{15}H_{22}Br_2$ requires C, 49.7; H, 6.1; Br, 44.2%).

5-*Keto*-8-*bromolongibornane* (**4**)

3-Ketolongifolene (**1**, 2.18 g) in dry ether (25 ml) was added dropwise to a stirred slurry of LAH (0.4 g) in ether (50 ml). At the end of reaction (3.5 hr; TLC:benzene) the mixture was successively treated with water (0.4 ml), 15% aq NaOH (0.4 ml) and water (1.2 ml). After stirring for another 15 min the granular precipitate was filtered off, washed thoroughly with ether, dried and solvent removed. The residue was refluxed with $CHCl_3$ containing 1 drop of 12*N* HCl (15 min.). The mixture was washed with water, dried, solvent removed and the residue chromatographed on silica gel/IIa (60 g; 46 cm × 2 cm): Fr. 1, light petroleum-benzene, 4 × 100 ml, transannular oxide (liquid, 0.61 g); and Fr. 2, benzene, 6 × 100 ml, pure.

Fr. 2 which solidified was recrystallized from light petroleum to furnish the 3β-alcohol (**8**), m.p. 108-9° (1.3 g). On acetylation with Ac_2O (10 ml) in pyridine (10 ml) at room temperature (16 hr) it gave the acetate (**9**) as a colourless liquid, b.p. 120° (bath)/0.9 mm (1.39 g); m.p. 71-72°; IR(nujol): 1740, 1660, 1260, 895; PMR(CCl_4): δ 4.93 (*m*, 1H, $-\overset{|}{C}HOAc$), 4.87 and 4.63 (two *s*, 1H each $>C=CH_2$) 2.67 (*m*, 1H, allylic H), 1.90 (*s*, 3H, $OCOCH_3$), 1.00, 0.97, 0.90 (three tertiary Me singlets); Mass: *m/z* 262 (M^+, base peak) (Found: C, 78.1; H, 10.1. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%).

A mixture of **9** (1.1 g) in 32% HBr-AcOH was kept at 30° for 18 hr and the isolated product hydrolysed with 10% methanolic KOH (10 ml) at room temperature overnight. The crude product was purified by chromatography over silica gel/IIb: Fr. 1, light petroleum-benzene, 2 × 50 ml, mixture. Fr. 2, benzene, 4 × 50 ml, pure bromoalcohol (**10**) (R = H), was recrystallized from light petroleum, m.p. 110-12° (0.55 g); IR(nujol): 3200, 1040, 780; PMR(CCl_4): δ 3.93 (*dd*, 1H, $HC-\overset{|}{C}HBr$), 3.30 (*m*, 1H, $-\overset{|}{C}HOH$); 1.13, 0.93, 0.83 × 2) (four tertiary Me singlets) (Found: C, 60.4; H, 8.6; Br, 26.1. $C_{15}H_{25}OBr$ requires C, 59.8; H, 8.3; Br, 26.5%).

Oxidation of **10** (R = H) (0.2 g) with Jones' reagent gave **4** as a colourless liquid (0.16 g); PMR(CCl_4): δ 3.63 (*dd*, 1H, $-\overset{|}{C}HBr$); 1.17, 1.13, 1.07, 0.90 (four tertiary Me singlets).

HBr addition to 11-*ketolongicyclene* (**3**): *Formation of* 11-*keto*-8-*bromolongibornane* (**6**)

A mixture of **3** (8 g) and 32% HBr-AcOH (50 ml) was kept at room temperature for 24 hr. The mixture was poured into water (250 ml), extracted with ether, washed with 5% aq Na_2CO_3, brine, dried and solvent removed. The crude solid was fractionally crystallized from EtOH to get the first crop of pure **6** as colourless needles, m.p. 178-79° (4 g, 36%); IR(nujol): 1750, 1420, 860, 780, 740. PMR(CCl_4): δ 4.20 (*dd*, 1H, $-\overset{|}{C}H-\overset{|}{C}HBr$, $J_1 = 6$ Hz, $J_2 = 2$ Hz), 1.10, 1.03, 1.00 × 2 (four tertiary Me singlets); Mass: *m/z* 298, 300 (M^+) (Found: C, 59.9; H, 7.8; Br, 26.6. $C_{15}H_{23}OBr$ requires C, 60.2; H, 7.7; Br, 26.8%).

A second crop of crystals, m.p. 120-30° (2.0 g) (obtained by addition of 5 ml of water to the filtrate) was found to be a mixture of **6** + 4-bromo-11-ketolongibornane. Further dilution of the filtrate with water (5 ml) gave the third crop of pure 4-bromo-11-ketolongibornane; IR(smear): 1750, 1420, 725; PMR(CCl_4): δ 3.90-4.83 (*m*, 1H, $-\overset{|}{C}HBr-CH_2-$), 1.10, 1.05, 1.00, 0.90 (four tertiary Me singlets); Mass: *m/z* 298, 300 (M^+) (Found: C, 60.0; H, 8.0; Br, 26.4. $C_{15}H_{23}OBr$ requires C, 60.2; H, 7.7; Br, 26.8%).

12-*Bromolongibornane*-3,4-*dione* (**13**)

To a stirred solution of TFA (207 g, 138 ml; 1.5 mol) cooled to 5-10° was added dropwise a solution of ω-

bromolongifolene (139 g; 0.5 mol) in CH_2Cl_2 (400 ml) during 1.5 hr; stirring was continued for 24 hr more at room temp. The mixture was quenched in ice-cold aq Na_2CO_3, the organic layer separated and the aqueous portion extracted with CH_2Cl_2 (3 × 200 ml). The combined organic extract was washed with brine, dried and solvent removed. The crude mixture (173 g) in EtOH (300 ml) was hydrolyzed with 15% aq ethanolic KOH (140 g of KOH in 100 ml of water and 700 ml of EtOH) at room temperature overnight. After removing most of the ethanol on a water-bath, the mixture was diluted with water (3 litres), extracted with EtOAc (3 × 500 ml), washed with brine, dried and solvent removed. The residue was carefully distilled at 1 mm at 150° (bath temp.) using a short vigreux column so that most of the unwanted bromoolefins mixture (12 g) was removed. The residue (129 g) consisting mostly of the bromoalcohol (**11**) was dissolved in acetone (600 ml) and oxidised with excess of Jones' reagent while stirring and cooling in an ice-bath; eight 100 ml portions of the reagent were added at intervals of 24 hr. The mixture was diluted with water, extracted with EtOAc (3 × 500 ml) and separated into acid (9 g, 9%) and neutral (105 g) fractions by extraction with 10% aq Na_2CO_3. The neutral material solidified and was recrystallized from light petroleum to give colourless needles of bromodiketone (**13**), m.p. 106-10° (29 g). The residue from filtrate was chromatographed on a column of silica gel/IIa (2.1 kg); Fr. 1, light petroleum, 4 × 500 ml, mixture of bromoolefins (19 g); Fr. 2, light petroleum-benzene (1:3), 6 × 500 ml, pure **13** (19 g, total yield 29 + 19 = 48 g, 42%); Fr. 3, benzene, 4 × 500 ml, mixture of **12** + **13**; and Fr. 4, benzene-EtOAc (9:1), 4 × 500 ml, pure 12-bromolongibornane-4-one (6 g, 6%).

12-Bromolongibornane-3,4-dione (**13**): m.p. 109-111° (light petroleum); IR(nujol): 1700, 1690, 995; PMR(CCl_4): δ 3.63 (AB *q*, 2H, $-CH_2Br$, J = 10 Hz), 1.13, 1.11, 1.01 (three tertiary Me singlets); Mass: *m/z* 312, 314 (M^+) (Found: C, 58.1; H, 6.9; Br, 26.2. $C_{15}H_{21}O_2Br$ requires C, 57.5; H, 6.7; Br, 25.5%).

12-Bromolongibornane-4-one (**12**): m.p. 72° (light petroleum); IR(nujol): 1700, 930; PMR(CCl_4): δ 3.29 (*q*, 2H, $-CH_2Br$, J = 12 Hz), 1.08, 1.00, 0.93 (three tertiary Me singlets); Mass: *m/z* 298, 300 (M^+) (Found: C, 60.8; H, 7.7; Br, 26.8. $C_{15}H_{23}OBr$ requires C, 60.2; H, 7.8; Br, 26.7%).

Na-K alloy reaction with 3-*keto*-8-*bromolongibornane* (**5**): *Formation of bicyclic keto-olefin* (**18**) *and* 3-*ketolongibornane* (**19**)

Na-K alloy (liquid, 1:5) was prepared by heating sodium (3 g) and potassium (15 g) in xylene until melted and carefully mixing the molten metals with a stirring rod and keeping the alloy in one large globule. On cooling the alloy remained liquid and 11.5 ml was pipetted out and transferred to a three-necked flask equipped with a dropping funnel, condenser and a N_2-gas inlet tube. To the stirred suspension of the alloy in dry ether (100 ml) was added dropwise a solution of **5** (11.5 g) in ether (200 ml). The mixture became dark blue during addition (1 hr). After 3 hr, 20% EtOH in light petroleum (250 ml) was added, poured into water, extracted with ether (3 × 100 ml), washed with brine, dried and solvent removed. The residue was dissolved in acetone (250 ml), treated with Jones' reagent (12 ml) and the isolated crude product (7 g) was chromatographed on 15% $AgNO_3$-silica gel (160 g; 54 cm × 3 cm): Fr. 1, light petroleum, 4 × 250 ml, 3-ketolongibornane (**19**), colourless liquid b.p. 100° (bath)/0.5 mm (2.95 g, 35%); IR(smear): 1695, 1435, 1160, 1060; PMR(CCl_4): δ 1.08, 1.02, 0.90, 0.77 (four tertiary Me singlets); Mass: *m/z* 220 (M^+ base peak) (Found: C, 82.0; H, 11.0. $C_{15}H_{24}O$ requires C, 81.8; H, 11.0%).

Fr. 2, light petroleum-benzene (1:3), 5 × 200 ml, bicyclic keto-olefin (**18**), colourless liquid, b.p. 130° (bath)/0.5 mm (2.85 g, 34%); IR(smear): 1700, 1410, 800; PMR(CCl_4): δ 5.22 (*bs*, 1H olefinic), 1.65 (*bs*, vinylic Me), 0.98 (*d*, 3H, CH*Me* J = 5 Hz), 1.03, 0.93 (two tertiary Me singlets); Mass: *m/z* 220 (M^+) (Found: C, 81.7; H, 11.1. $C_{15}H_{24}O$ requires C, 81.8; H, 11.0%).

Na-K alloy reaction on 5-*keto*-8-*bromolongibornane* (**4**): *Formation of* 5-*ketolongibornane* (**15**)

Compound (**4**, 0.68 g) in dry ether (50 ml) was reacted with Na-K alloy (0.7 ml) as described for **5**; in this case no blue colour was formed during the reaction. Theisolated product was distilled to give a colourless liquid, b.p. 130° (bath)/0.6 mm (0.5 g, 95%) which was characterized as pure **15**; IR(smear): 1730, 1690, 1435; PMR(CCl_4): δ 0.83, 0.86, 0.90, 1.06 (four tertiary Me singlets). (Found: C, 81.4; H, 10.4. $C_{15}H_{24}O$ requires C, 81.8; H, 11.0%).

Na-K alloy reaction on 11-*keto*-8-*bromolongibornane* (**6**): *Formation of* 11-*ketolongibornane* (**17**)

Compound (**6**, 0.5 g) in dry ether (50 ml) was reacted with Na-K alloy (0.5 ml) in the usual manner. On distillation, a colourless liquid, b.p. 125° (bath) 0.5 mm (0.31 g, 85%), m.p. 55°, characterized as pure **17** was obtained; IR(nujol): 1740, 1420, 1200, 1170, 1060; PMR(CCl_4): δ 1.05 × 2, 0.90, 0.83 (four tertiary Me singlets) (Found: C, 81.8; H, 11.4. $C_{15}H_{24}O$ requires C, 81.8; H, 11.0%).

Na-K alloy reaction on 12-*bromolongibornane*-3,4-*dione* (**13**): *Formation of bicyclic vinylidenedione* (**21**)

13 (3.16 g) in dry ether (100 ml) was reacted with Na-K alloy (4 ml) in the usual fashion. The complex

mixture (TLC; 1.98 g) isolated in this case was chromatographed on silica gel (60 g; 48 cm × 1 cm): Fr. 1, benzene, 4 × 100 ml, pure; Fr. 2, benzene-EtOAc (98:2), 3 × 100 ml, mixture; and Fr. 3, benzene-EtOAc (90:10), 4 × 100 ml, mixture.

Fr. 2 was distilled to furnish **21** as a pale yellow liquid, b.p. 160° (bath)/0.5 mm (0.28 g, 15%); IR(smear): 3060, 1700, 1645, 1410, 885. PMR(CCl_4): δ 4.77, 4.68 (two *s*, 1H each, $>C=CH_2$), 1.18 (*d*, 3H, *sec-Me*, $J=5$ Hz), 1.10, 1.07 (two tertiary Me singlets); Mass:*m/z* 234 (Found: C, 78.8; H, 10.5. $C_{15}H_{22}O_2$ requires C, 76.8; H, 9.5%).

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Metal-catalyzed Oxidations of α-Pinene & Car-3-ene†

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The cobalt naphthenate-catalyzed autoxidation of α-pinene and car-3-ene has been investigated using a modified method. Two major reactions, the allylic oxidation and epoxide formation have been observed. The product composition can be rationalized by considering (i) electronic factors involved in the stabilization of radicals, (ii) the geometry of the allylic hydrogen, and (iii) the effect of dihedral angle between substituents on the double bond and the hydrogens on the adjacent carbon in the allylic radical. The importance of the last factor has not been appreciated earlier. The present method affords a simple preparative method for *trans*-verbenol, verbenone and *cis*-verbenol (via $LiAlH_4$ reduction of verbenone) from α-pinene and for car-3-en-5-one from car-3-ene.

Several studies on the autoxidation of α-pinene[2-7] and car-3-ene[8-15] have been reported by earlier workers. The emphasis has been on isolation and identification of the products formed even in minor amounts. However, no attempts were made to modify and innovate the autoxidation step to make it a useful preparative method for some of the products formed, which are otherwise not easily accessible by alternate routes. This paper deals with the attempts made in this direction. In addition, we have tried to rationalize the composition of oxidation products based on (i) electronic factors involved in the stabilization of radicals, (ii) geometry of the allylic hydrogen, and (iii) the effect of dihedral angle between substituents on the double bond and the hydrogens on the adjacent carbon in the allylic radical.

In a gas-liquid reaction of autoxidation type, the reaction rates would be considerably enhanced by increasing the surface area where the two reactants come in contact (gas-liquid interface) in the presence of a ctalyst. Hence, a special reactor originally designed by Vodnar[16], was modified and fabricated for the present study. This reactor has been so designed that the oxygen gas bubbling through the substrate entrains the liquid and carries it upwards through a spiral tube where it is thrown against the sides of the tube to form a liquid-gas interface over a large area where the reaction actually takes place. After the separation of oxygen, the liquid returns through a capillary to the reactor tank.

In the present study cobalt naphthenate was used to catalyse the oxidations of neat liquids (α-pinene and car-3-ene). These conditions are similar to those reported by us earlier on oxidation of 1-phenylcycloalkenes[1].

The cobalt-catalyzed oxidation of α-pinene gave *trans*-verbenol and verbenone in 12 and 40% yields respectively besides a few other compounds including α-pinene epoxide (12%). The verbenone on $LiAlH_4$ reduction gave exclusively *cis*-verbenol. The *trans*-verbenol is easily converted into verbenone by pyridinium dichromate oxidation, thereby increasing the overall yields of verbenone and ultimately *cis*-verbenol (60%).

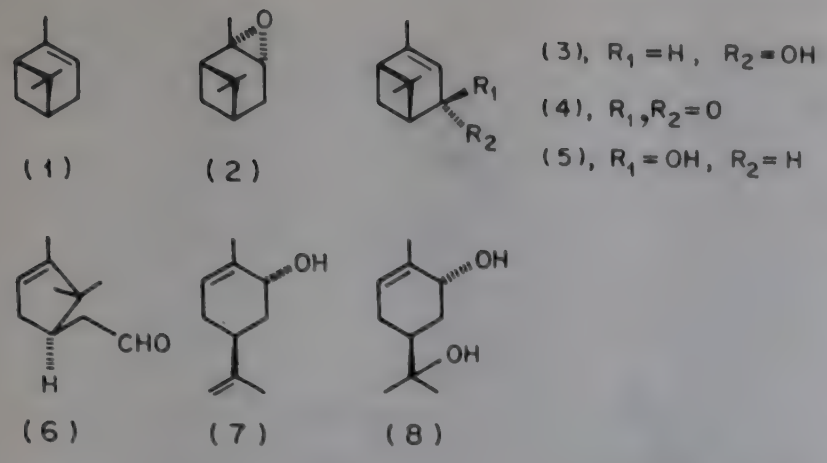
Earlier reports on the autoxidation of car-3-ene[14,15] indicate that the opening of cyclopropane ring was a major phenomenon as shown by most of the compounds isolated. The reaction conditions have now been modified so as to yield mostly the primary products of car-3-ene autoxidation, that is compounds with cyclopropane ring intact. The products isolated in good yields were car-2-en-4-one, car-3-en-5-one and car-3-ene-2,5-dione.

Some of the compounds available from the autoxidation of car-3-ene and α-pinene have been recommended for controlling the insects[17].

Oxidation of α-pinene (1)

Oxidation of **1** using cobalt naphthenate as catalyst at 50° for 36 hr resulted in 85% conversion. GLC (FFAP column) of the total mixture showed the presence of six components with $t_R = 1.0$ (12.1%), 1.42 (13.7%), 1.84 (8.6%), 2.58 (20.6%), 3.53 (39.5%), and 4.42 (5.5%). The components with $t_R = 1.0$, 2.58 and 3.53 were isolated in pure form by column chromatography on alumina. These compounds were identified by their spectral data as α-pinene epoxide (**2**), *trans*-verbenol (**3**) and verbenone (**4**).

†NCL Communication No. 3569.



The identity of **2** was confirmed by direct comparison (IR, PMR) with an authentic sample prepared using monoperphthalic acid[18]. The identities of **3** and **4** were confirmed by comparison with the reported[19] spectral data. In the case of **4**, the identity was further confirmed by preparation of the semicarbazone (m.p. 203°; lit.[20], m.p. 203-5°). The identity of **3** was also confirmed by its oxidation to **4**. That *cis*-verbenol (**5**) was not formed in this reaction, was demonstrated by co-GLC with an authentic sample obtained by $LiAlH_4$ reduction of verbenone.

However, column chromatography on silica-gel resulted in the isolation of compounds with $t_R = 1.42$, 3.53, and 4.42. These compounds were identified as α-campholene aldehyde (**6**), verbenone (**4**), and *trans*-carveol (**7**), respectively. Apart from these three compounds, a solid product (m.p. 145-46°) was also isolated and identified as *trans*-sobrerol (**8**). The identities of **6**, **7** and **8** were established by their spectral data. In the case of **6** and **8** the identity was further established by comparison (IR, PMR) with authentic samples prepared from α-pinene epoxide by standard methods[2,21,22]. The identity of **7** was also established by comparison (IR, PMR) with the available authentic sample. Since it is known[23] that α-pinene epoxide on silica-gel gives **6**, **7** and **8**, these compounds are not the products of autoxidation. Presumably, similar reactions are also taking place on GLC column[24]. Thus, it can be concluded that only three products, viz. **2**, **3** and **4** were formed in the autoxidation of α-pinene. Withdrawal of aliquots during reaction followed by work-up and GLC analysis demonstrated that initially alcohol **3** was the major product and subsequently this was converted into the ketone **4**.

Oxidation of car-3-ene (9)

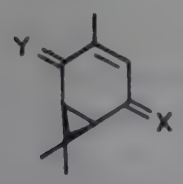
The most exhaustive work on the autoxidation of **9** has been due to Baines and Cocker[14]. These workers isolated several products from the autoxidation using cobalt stearate as catalyst. The product mixture was worked up under different experimental conditions. In none of the cases less than ten compounds were isolated. In an earlier work from this laboratory, Sharma[15] reported the formation of ten compounds from the autoxidation of **9** using cobalt naphthenate as catalyst. Five of the compounds isolated were obtained as a result of cyclopropane ring opening. One of the objectives in the present work was to obtain the primary products of autoxidation. It was anticipated that most of these should have the cyclopropane ring intact.

Autoxidation of **9** in the Vodnar reactor[16] using cobalt naphthenate as catalyst gave after usual work-up (sodium sulphite) a mixture of five compounds [$t_R = 1.0$ (23.9%), 2.14 (20%), 3.0 (8.7%), 6.14 (37.8%), and 7.14 (9.6%)] as determined by GLC (QF_1 column). These products were isolated by column chromatography, inverted dry column chromatography[25] and/or by preparative GLC from the reaction mixture. The compounds with $t_R = 2.14$, 3.0, 6.14, and 7.14 were readily identified on the basis of their spectral data as **10**, **13**, **11** and **12** respectively.

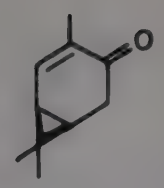
Their identities were further confirmed by comparison of their spectral data with those reported[26] in literature. The liquid product with $t_R = 1.0$ appeared from its spectral data (IR, PMR) and mode of formation to have the structure **14** or **15**. The PMR data reported earlier[14,27,28] for both of these compounds suggests that the autoxidation product ($t_R = 1.0$) is probably **14**. This was confirmed by a reaction described later.

Apart from these compounds, a minor component ($t_R \sim 1.0$, often merged on GLC with compound $t_R = 1.0$) was also isolated. It had spectral (IR, PMR) data very similar to those reported[26] for **16**. It may be pointed out that the PMR spectrum readily differentiates **16** from the isomeric compound **17**. The formation of **16** also suggests that the component with $t_R = 1.0$ is most probably **14**. A direct confirmation of this was obtained by autoxidation of the compound with $t_R = 1.0$ under usual conditions. Such an autoxidation furnished a product identical in every respect with **16** ($t_R \sim 1.0$) which was isolated as the minor product of autoxidation. This correlation established the strucutre of the autoxidation product with $t_R = 1.0$ as **14**. Further, Baines and Cocker[14] have earlier observed that compound **14** even when stored at room temperature gets converted into **16**.

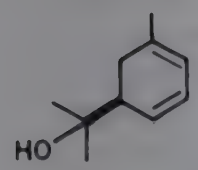
It is worth noting that only six compounds are formed in the autoxidation of **9** and of these the compounds having cyclopropane ring intact form the bulk (75%). The effects of altering the autoxidation conditions are given in Table 1. Examination of Table 1 reveals that the sum of the percentages of the products **12** and **13** is ~17% in all experiments. This seems to indicate that the diketone **12** probably arises from the monoketone **13** rather than from **11**.



(9), $X = H_2$, $Y = H_2$
(11), $X = O$, $Y = H_2$
(12), $X = Y = O$
(13), $X = H_2$, $Y = O$

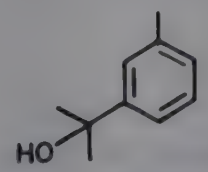


(10)



(14)

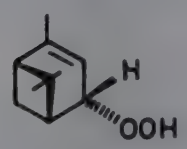
(15)



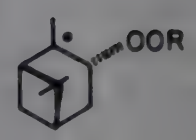
(16)

(17)

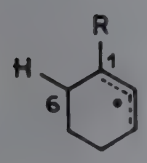
(18)



(19)

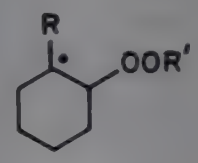


(20)



(21a), $R = CH_3$
(31a), $R = Ph$

(21b), $R = CH_3$
(31b), $R = Ph$



(22), $R = CH_3$
(32), $R = Ph$

Table 1—Product Composition (%) by GLC in the Cobalt Naphthenate-catalysed Autoxidation of Car-3-ene (neat, 1% catalyst)

Product	Autoxidation conditions		
	25°/6 hr	5°/5 hr	−2°/60 hr
14	23.9	24.7	22.2
16	Traces	Traces	Traces
10	20.0	15.8	14.6
13	8.7	15.8	10.5
11	37.8	42.0	46.0
12	9.6	1.7	6.7
Conversion	82.6	64.0	86.0

Discussion

α-Pinene autoxidation

(a) *Stereochemistry of the products*: It is well known[29] that in pinene series most reagents attack from the less hindered α-face. In agreement with this the allylic radical (**18**) will be attacked from α-face to give the hydroperoxide (**19**) which on work-up affords **3**. In a similar fashion, addition to the double bond affords the radical **20** which furnishes the epoxide **2**.

(b) *Comparison of results obtained on autoxidation in α-pinene with those obtained in 1-methylcyclohexene*: It has been shown[15] that 1-methylcyclohexene affords 29% products derived from epoxide and 60% products from allylic oxidation (see Table 2). These results are very similar to those obtained in the autoxidation of α-pinene [epoxide derived (**2**+**6**+**7**) 31%, allylic oxidation (**3**+**4**) 60%]. Both radicals **18** (formed by H-abstraction) and **20** (formed by addition) are essentially the cyclobutylcarbinyl radicals and hence in both cases the contribution of cyclobutane ring to the stability of the two radicals would be the same. Based on these considerations, energy difference between **18** and **20** and the transition states leading to them should be the same as energy difference between **21** and **22** and the transition states leading to them. Hence, electronic

Table 2—Ratio of Epoxide Derived Products to Those from Allylic Oxidation (E:A)

Compound	E:A Ratio	Reference
1-Methylcyclohexene	29:60	15
1-Methylcyclohexene	31:62	Present work
α-Pinene	31:60	Present work

factors would lead to the anticipation that autoxidation of both the substrates should be similar.

If one looks at the geometry of the allylic hydrogens, one could anticipate that in 1-methylcyclohexene both allylic radicals (**21a** and **21b**) should be readily formed, whereas in case of α-pinene the other allylic radical (**23**) cannot be formed since the concerned hydrogen is orthogonal to the π-clouds of the double bond. In agreement with this, the allylic oxidation in 1-methylcyclohexene gives both the isomeric allylic alcohols **24** and **25** and both the α,β-unsaturated ketones **26** and **27**.

On the contrary, in α-pinene, as expected, no product derived from the radical **23** is obtained. Thus, the geometry of the allylic hydrogen should be expected to result in a lesser amount of allylic oxidation in α-pinene as compared to 1-methylcyclohexene. Since the observed results do not reflect this feature some other factor must be involved. In our opinion, this factor is the ease of approach in epoxide formation. In the case of α-pinene, epoxide formation can take place only from one face, i.e. α-face, whereas in 1-methylcyclohexene, epoxide formation can take place from both faces. Thus, α-pinene undergoes epoxide formation from one face and allylic oxidation at one site; however, in 1-methylcyclohexene the epoxide formation can take place from two faces and allylic oxidation at two sites. Hence, the ratio between the products derived from epoxide and those from allylic oxidation (i.e. E:A) in the two cases (α-pinene and 1-methylcyclohexene) remains the same.

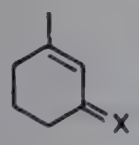
Another factor that may be considered is the eclipsing of substituents during the formation of radicals **18** and **21a**. Examination of Drieding models show that in the preferred conformation[29–31] (**1a**) of α-pinene, the C-2 methyl almost eclipses the C-1 hydrogen ($\varphi \sim 5°$), whereas in the radical **18** this dihedral angle remains practically unaltered ($\varphi \sim 5°$). In 1-methylcyclohexene also the dihedral angle between C-1 methyl and C-6 hydrogen ($\varphi \sim 45°$) remains unaltered ($\varphi \sim 45°$) in the formation of radical **21a**. Thus, it is obvious that this factor does not affect the two reactions. However, this factor is important in the autoxidation of car-3-ene (*vide infra*).

(c) *Comparison of different catalysts used in autoxidation*: The ratio of epoxide derived products to products of allylic oxidation (E:A) in the present study is 0.5. However, earlier workers[5,6] have observed quite different E:A ratios using other cobalt derivatives eventhough the other conditions are nearly the same (liq. phase, 50°C). Thus, E:A ratio with cobalt abietate was 0.14[5] whereas with polychelates of Co(II) it was 0.11[6]. This obviously suggests that the anion of the catalyst plays an important role in autoxidation.

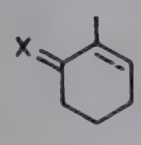
Car-3-ene autoxidation

(a) *Absence of epoxide derived products*: The major difference in the autoxidation of car-3-ene as compared to either α-pinene or 1-methylcyclohexene is the total absence of epoxide and epoxide derived products in the case of car-3-ene. In earlier reports also[14] epoxide formation was a minor reaction in the autoxidation of car-3-ene. The failure to obtain epoxide derived products can be explained by comparing the stability of the radicals **28** and **29** formed by hydrogen abstraction with the radical **30** obtained by addition. In radicals **28** and **29** there is stabilisation due to conjugation with double bond as well as with the cyclopropane ring. The radical **30** formed by addition has no such stabilisation, and therefore the energy difference between **28**/**29** and **30** and the transitions states leading to them is much

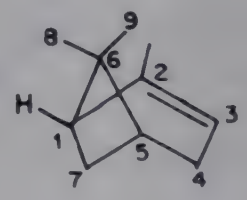
(23)



(24), X=H, OH
(26), X=O



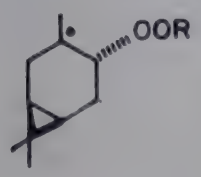
(25), X=H, OH
(27), X=O



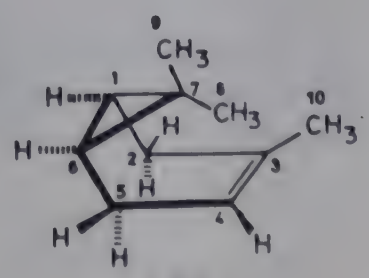
(1a)

(28)

(29)



(30)



(33)

larger than the energy difference between the corresponding radicals **18** and **20** in the pinene series.

In the case of 1-phenylcyclohexene[1] the radical **32** derived by addition will now be greatly stabilised as compared to the corresponding radical **22** in 1-methylcyclohexene. As a result the E:A ratio in 1-phenylcyclohexene is ~8.0. It may be pointed out that the phenyl group does not stabilize the radicals **31a** and **31b** appreciably.

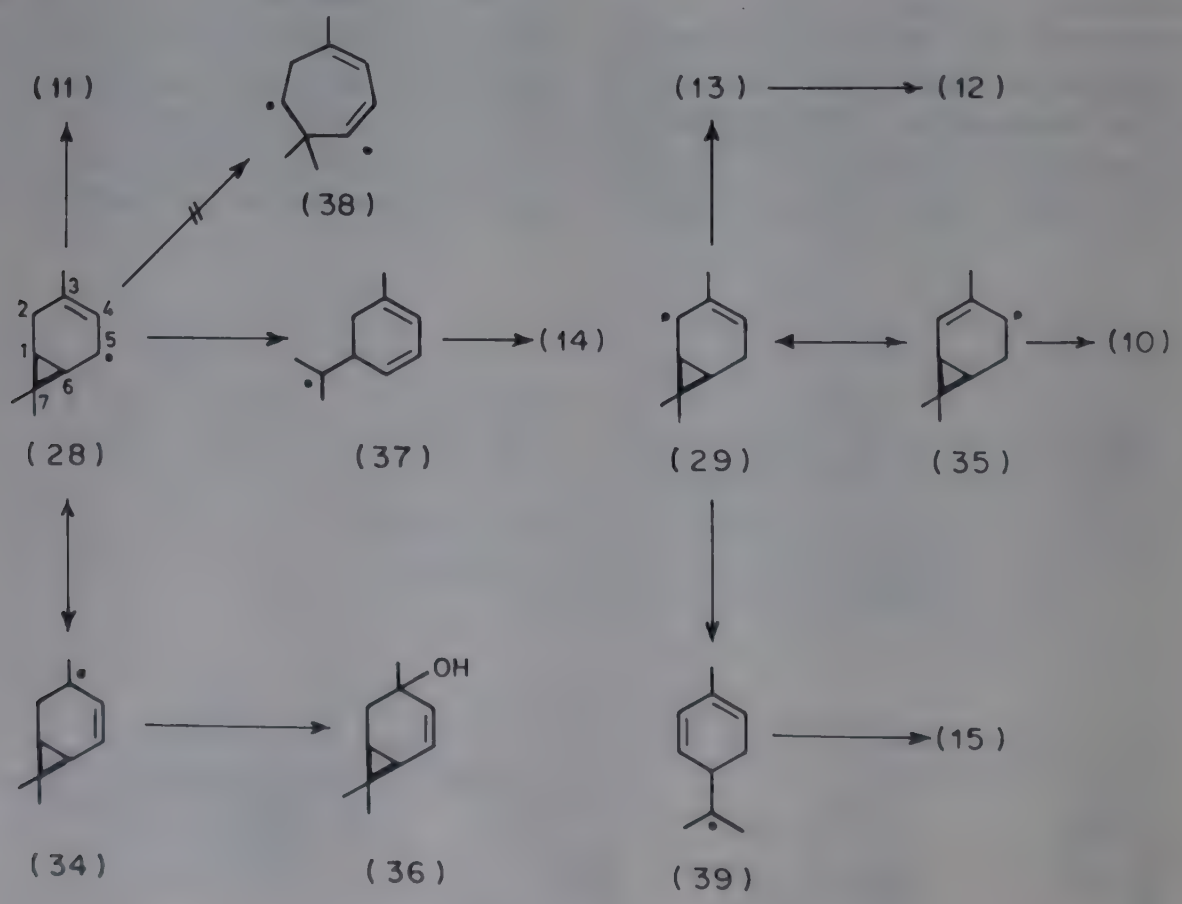
(b) *Difference in percentage of products derived from radicals* **28** *and* **29**: Another feature that enhances the stabilization of the radicals **28** and **29** as compared to **30** is the steric effect. In the preferred conformation[32] (**33**) of car-3-ene the C-3 methyl group makes a dihedral angle of ~20° with the quasi-equatorial hydrogen at C-2. In the radical **28** this dihedral angle increases to ~30°, resulting in a strain relief which also favours allylic oxidation. On the contrary, conversion of 1-methylcyclohexene to the radical **21a** is accompanied by no change in steric strain (dihedral angle in both ~45°). In radical **29** the dihedral angle between C-4 hydrogen and the equatorial C-5 hydrogen is ~30° whereas in car-3-ene it is ~20°. A similar kind of strain relief is expected in the transition states leading to **28** and **29**. Thus, it can be realised that the conversion of car-3-ene to **28** (relief of methyl-hydrogen eclipsing interaction) would be more favoured due to this factor than the conversion of car-3-ene to **29** (relief of hydrogen-hydrogen eclipsing interaction). This readily explains why the products **11** and **14** derived from radical **28** are in larger percentage (62-68%) than the products **13**, **12** and **10** derived from radical **29** (38-31%) (see Scheme 1).

It can be rationalized by recent observations that the radical attack at secondary positions is preferred to the attack at tertiary ones due to steric reasons[33]. This also explains why no tertiary products are obtained in autoxidation of 1-methylcyclohexene[15], 1-phenylcyclohexene[1] or α-pinene.

(c) *Formation of the cyclohexadiene* (**14**): Compound **14** is obviously formed from **28** through the radical **37** by the usual rearrangement of cyclopropylcarbinyl radical to homoallylic radical. The alternate rearrangement of **28** to the doubly homoallylic radical (**38**) does not take place since the C_1-C_6 bond is orthogonal to the *p*-lobe of the radical at C-5. However, in the conversion of **28** to **37** the C_6-C_7 bond is suitably placed for overlap. The failure to obtain **15** from radical **29** through the intermediacy of radical **39** cannot be explained. Such a change (**29**→**39**) is also favoured by the geometry of the concerned orbitals.

Experimental Procedure

All m.ps and b.ps are uncorrected. UV spectra were recorded on a Carl-Zeiss 44069 spectrophotometer, IR spectra on a Perkin-Elmer 137-E spectrophotometer, PMR spectra on a Varian T-60 spectrophotometer using TMS as internal standard and mass spectra on a



SCHEME 1

CEC-21-110B spectrometer. Analytical and preparative GLC of the reaction products were carried on an Aerograph A-350-B chromatograph using columns (a) 20% FFAP (carbowax 20M reacted with nitroterephthalic acid) adsorbed on chromosorb W (60-80 mesh) packed in 6′ × 1/4″ aluminium column, (b) 5% QF_1 (5% fluorinated silicon QF_1) adsorbed on chromosorb W HMDS (60-80 mesh) packed in 5′ × 1/4″ aluminium column, and (c) preparative FFAP: 30% FFAP adsorbed on chromosorb W (30-60 mesh) packed in 12′ × 3/8″ aluminium column. The relative retention times (t_R) refer to the ratios of retention time of the products as compared with the peak of lowest retention time in each chromatogram. Silica-gel (grade-II) and alumina (grade-II) were prepared according to the method of Hernandez *et al.*[34].

Car-3-ene and α-pinene were freshly distilled under reduced pressure (35-40 mm) over sodium.

Autoxidation of α-pinene (1)

α-Pinene (56 g) containing cobalt naphthenate (0.56 g, cobalt content 9%) was subjected to autoxidation in a Vodnar reactor[16] immersed in an oil-bath at 50°. Dry oxygen gas (after passing through conc. H_2SO_4 and KOH traps) was then bubbled at a rate of 3-4 litres/hr. Aliquots were removed after 10, 20, 27 and 36 hr, and analysed by GLC on FFAP column (125° C; H, 60-80 ml/min). After 36 hr, reaction was stopped and the reaction mixture stirred with saturated Na_2SO_3 solution (~55 g in H_2O) at room temperature for 2-3 hr, and extracted with ether (3 × 100 ml). The ethereal layer was washed with water, dried (anhydr. Na_2SO_4) and solvent removed to give a yellow liquid (~50 g). Part of this material after work-up was distilled (110° C, oil-bath, 40 mm) to give about 11-13% of **1**. Thus, the percentage conversion was 87-89%.

Resolution of product mixture

(a) A part of the total material after work-up (6.6 g) was subjected to column chromatography over silica-gel (grade-II, 187 g). All major fractions were checked by GLC (FFAP column, 125°C; H_2, 60-80 ml/min).

A compound corresponding to peak-5 (t_R = 3.53) was obtained in pure state [0.73 g, obtained from fraction eluted with benzene-ethyl acetate (9.5:0.5)] and characterized as verbenone (**4**) on the basus of its spectral data[19] [b.p. 95° (oil-bath)/2 mm (Lit.[20], b.p. 110-15°/16 mm, M^+ 150; semicarbazone: m.p. 203° (from ethanol-water), lit.[20], m.p. 203-5°].

The fraction corresponding to second peak (t_R = 1.42) on GLC was eluted with pet. ether (60-80°)-benzene (4:6) and purified by inverted dry column chromatography [dry packing, TLC silica-gel, ethyl acetate-benzene (0.2:9.8) as eluent] to give a compound (0.26 g) which was identified as α-campholene aldehyde (**6**) [b.p. 78°C/10 mm (lit.[20], b.p. 85°/14 mm), M^+ 152] on the basis of spectral data. Its identity was confirmed by direct comparison (IR, PMR) with an authentic sample prepared by the action of anhyd. $ZnBr_2$ on α-pinene epoxide (**2**)[21].

Another fraction [0.55 g, benzene-ethyl acetate (9.5:0.5)] from the above chromatography was found to be a mixture of three compounds (GLC). It was resolved by preparative GLC on FFAP preparative column (125°C; H_2, 120 ml/min). Out of the two fractions collected, one fraction was containing a major compound (~90%) mixing with peak-6 (t_R = 4.42). Based on its spectral data and comparison with those reported in literature, this compound was identified as *trans*-carveol (**7**) [b.p. 90° (oil-bath)/3 mm; lit.[35a], b.p. 80°/4 mm].

The substance obtained from ether fraction solidified on keeping. It was washed with ether to get a clear solid which recrystallised from benzene to furnish crystals of *trans*-sobrerol (**8**) (0.20 g), m.p. 145-46° (lit.[20], m.p. 146-47°), M^+ 170. The identity was confirmed by direct comparison (IR, m.p., m.m.p.) with an authentic sample prepared by the action of aq. acid on α-pinene epoxide (**2**)[2,22].

(b) The autoxidation product (4.05 g) was chromatographed on neutral alumina (grade-II, 120 g). The fraction (0.110 g) eluted with pet. ether (60-80°) gave only one peak on GLC (QF_1 column). The spectral data indicated this compound to be a pure sample of **2** [b.p. 91-93°/27 mm, (lit.[18], b.p. 81°/21 mm); M^+ 152]. However, this compound gave two peaks on FFAP column due to partial conversion to the aldehyde **6**. The identity was confirmed by direct comparison (GLC, IR, PMR[24]) with an authentic sample of **2** prepared from α-pinene using monoperphthalic acid[18].

The fraction (0.287 g) eluted with pet. ether (60-80°)-benzene (3:7) was purified by fractional distillation. The first fraction (110°C, oil-bath/2 mm) gave a pure compound (M^+ 152) corresponding to peak-4 (t_R = 2.58) on GLC. From the mode of formation and spectral data this product appeared to be verbenol. Comparison of its PMR data with those of a reported[19] sample showed it to be *trans*-verbenol (**3**). The identity was confirmed by its oxidation (pyridinium dichromate)[36] to verbenone (**4**). In agreement with its *trans*-geometry, the autoxidation product was shown to be different from a sample of *cis*-verbenol (**5**) prepared by reduction of verbenone (**4**) using $LiAlH_4$[19].

The fraction eluted with pet. ether (60-80°)-benzene (9:1) on distillation gave a compound (0.26 g) which on comparison of its spectral data (IR, PMR) was found

to be identical with verbenone (**4**) [b.p. 95° (oil-bath)/ 2mm, lit.[20], b.p. 110-15°/16 mm]. The identity was confirmed by direct comparison (co-GLC, IR) with a sample prepared from the oxidation of **3**.

Autoxidation of car-3-ene (9)

Car-3-ene (5.52 g) containing cobalt naphthenate (0.55 g) was autoxidized at 25° in a small Vodnar reactor by bubbling dry oxygen gas. Initially the gas flow was 1-2 litres/hr but after 2 hr it was increased to 5-6 litres/hr. Reaction was stopped after 6 hr and the mixture worked-up as in the case of α-pinene. After removal of solvent a yellow liquid (5.49 g) was obtained which in GLC on QF_1 column (90°C; H_2, 90-100 ml/ min) was found to be a mixture of five compounds.

The total material (4.096 g) was subjected to column chromatography over silica-gel (grade-II, 192 g). All major fractions were checked by GLC (QF_1 column, 90°C; H_2, 90-100 ml/min) along with the total material. Recovered 3-carene (elution with pet. ether) was 17.5%, and hence percentage conversion was 82.5.

The fraction eluted with benzene-ethyl acetate (8:2) gave a pure compound (0.58 g; b.p. 61°/0.5 mm; M^+ 150), corresponding to peak-4 ($t_R = 6.14$) on GLC of the total material. It was identified as car-3-en-5-one (**11**) (lit.[26], b.p. 58°/0.5 mm) by comparison of its spectral data with those reported in literature[26].

The fraction (0.4 g) eluted with benzene-ethyl acetate (9:1) was subjected to chromatographic separation on silica-gel [21 g, TLC grade, dry packing, elution with benzene-ethyl acetate (97.5: 2.5)] when a pure compound [b.p. 65-66°/0.5 mm (lit.[26], b.p. 60-75°/0.5 mm); M^+ 150] corresponding to second peak on GLC ($t_R = 2.14$) was obtained. Based on spectral data it was identified as car-2-en-4-one (**10**)[25].

The fraction (0.2 g) eluted with benzene-ethyl acetate (9:1) was also subjected to chromatographic separation on silica-gel [8-10 g, TLC grade, dry packing, elution with benzene-ethylacetate (98:2)] when a pure compound [m.p. 94 (from ethanol)] corresponding to peak-5 ($t_R = 7.14$) on GLC of the total product mixture was obtained. Its spectral data were found to be identical with those of car-3-ene-2,5-dione (**12**) (lit.[26], m.p. 94-95) given in literature[26].

The fraction (0.4 g) eluted with benzene-ethyl acetate (9.5:0.5) on preparative GLC (preparative FFAP, 235 C; H_2, 110 ml/ min) gave four cuts (A-D). Fraction-C on purification by column chromatography gave a pure compound (0.070 g, b.p. 68-70°/0.5 mm; M^+ 152) corresponding to first peak ($t_R = 1.0$) on GLC of the total mixture. Based on spectral data it was suspected to be 1-methyl-5-(α-hydroxyisopropyl)cyclohexa-1,3-diene (**14**). The identity was confirmed by comparison of spectral data with those reported for **14**[14]. Fraction-D was found to be a mixture of two compounds. It was separated by column chromatography over silica-gel. The minor compound ($t_R \sim 1.0$) was isolated (0.050 g) and identified as 8-hydroxy-*m*-cymene (**16**, M^+ 150) by comparison of its spectral data with those reported in literature[26]. The major compound isolated in pure state [0.180 g, b.p. 65-70°/0.5 mm (lit.[25], b.p. 60-75°/ 0.5 mm); M^+ 150] from fraction-D was found to be car-3-en-2-one (**13**) by comparison of its spectral data with those reported in literature[26]. It corresponded to third peak ($t_R = 3.0$) on GLC of the total mixture.

Autoxidation of car-3-ene was also carried out at lower temperatures 5° (5.53 g, cobalt naphthenate 0.056 g, 5 hr) and −2° (5.47 g, cobalt naphthenate 0.055 g, 60 hr). Method of work-up was the same as in earlier experiment. Percentage conversion and product composition under these conditions are shown in Table 1.

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A Facile Synthesis of 7-Methoxyisochroman-3-one: Synthesis of 2,3-Dialkoxy-10-methoxyberbines

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An easy two-step synthesis of 7-methoxyisochroman-3-one (**2**) is described starting from 4-methoxy-N,N-dimethylbenzylamine. The synthetic utility of **2** is demonstrated by synthesising two new 2,3-dialkoxy-10-methoxyberbines (**5a** and **5b**).

Isochroman-3-ones are valuable synthons for isoquinolines and berbines, and for the construction of various heterocyclic ring systems[1-3]. A most interesting use of isochroman-3-ones is that they provide benzocyclobutenes, which are useful intermediates for the synthesis of a large number of carbocyclic and heterocyclic compounds[4].

7-Methoxyisochroman-3-one (**2**) has been found useful for the synthesis of steroidal harmones. Though it was first used[5] in 1980, its preparation and properties were not reported. At the moment a four-step[6] and a six-step[7] syntheses of **2** are available. In the four-step approach the final product is obtained as a mixture of isomers from which the desired isomer has to be separated by chromatography. In the present paper we report a simple two-step synthesis of **2** (see Scheme 1), involving heteroatom-directed metalation reaction[8] as the key step.

4-Methoxy-N,N-dimethylbenzylamine was lithiated[9] with *n*-BuLi and the litho-derivative reacted with paraformaldehyde to give the aminoalcohol (**1**) in 58% yield, characterized by its IR and PMR spectra (see Experimental). The amino alcohol (**1**) was then converted into 7-methoxyisochroman-3-one (**2**) by reacting it successively with ClCOOEt, KCN, alc. KOH and finally with hydrochloric acid. Its IR and PMR spectral data are in agreement with those reported in literature[6,7].

We have now demonstrated the utility of **2** for the synthesis of two new 10-methoxyberbines (**5a** and **5b**) as shown in Scheme 2. So far no synthesis of 10-methoxyberbines has been reported, probably because of difficulties to synthesise these by normal methods involving Bischler-Napieralski and Mannich cyclisations.

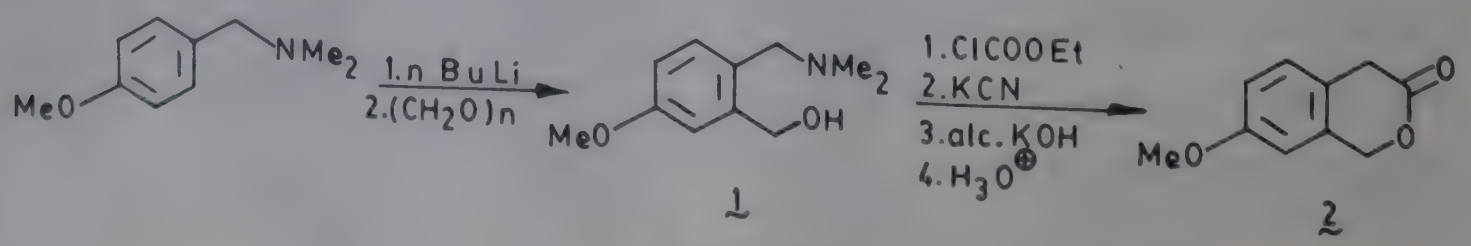
The isochromanone (**2**) was condensed with homoveratryl amine (**3a**) and homopiperonyl amine (**3b**) to provide hydroxyamides (**4a**) and (**4b**) in 82 and 75% yields respectively. Bischlar-Napieralski cyclisation of **4a** and **4b** with PCl_5 followed by $NaBH_4$ reduction provided **5a** and **5b** respectively. The structures of all these compounds were established on the basis of analytical and spectral data.

Experimental Procedure

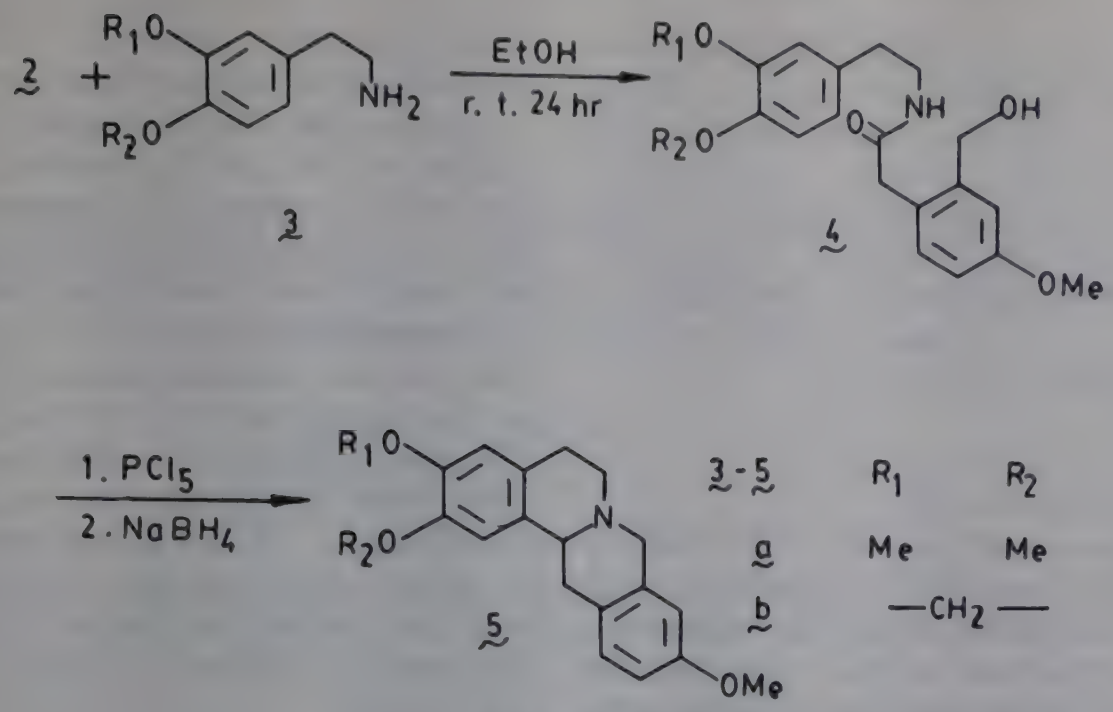
All m.ps are uncorrected. IR spectrum (ν_{max} in cm^{-1}) were recorded in nujol on a Beckman IR-20 spectrophotometer, UV (λ_{max} in nm) in MeOH on a Shimadzu UV-300 spectrophotometer and PMR spectra in $CDCl_3$ on a Perkin-Elmer R-32, 90 MHz instrument; chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard.

3-Methoxy-6-dimethylaminomethylbenzenemethanol (**1**)

A solution of 4-methoxy-N,N-dimethylbenzylamine (4.960 g, 0.03 mol) in ether (25 ml) was stirred at 0° and *n*-butyllithium (0.09 mol [prepared from lithium (1.4 g) and of *n*-butyl bromide (10.2 ml) in ether (100 ml)] was added to it during 10 min. The reaction mixture stirred at room temperature for 24 hr and paraformaldehyde (10 g) added to it in lots during 20



Scheme 1



Scheme 2

min. Initially a vigorous reaction was observed. The reaction mixture was stirred for 2 hr, decomposed with water (50 ml), the organic layer separated and the aqueous layer extracted with ether (3 × 50 ml). The combined ether extract was treated with 1:1 HCl (3 × 25 ml), the acidic layer basified with 2 *N* NaOH and extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated to give an oily product, which was distilled under reduced pressure to furnish **1** (3.35 g, 58%), b.p. 158°/3 mm; IR (neat): 3400 and 3200 (OH); PMR(CCl_4): 2.14 (*s*, 6H, NMe_2), 3.33 (*s*, 2H, Ar $-CH_2-$N), 3.70 (*s*, 3H, OMe), 4.32 (*s*, 2H, Ar$-CH_2-$O), 5.65 (*bs*, 1H, OH, exchangeable with D_2O), 6.56 (*dd*, J=8 and 2.5 Hz, 1H, Ar−H), 6.73 (*d*, J=2.5 Hz, 1H, Ar−H), 6.95 (*d*, J=8 Hz, 1H, Ar−H) (Found: C, 67.3; H, 8.8. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8%).

7-*Methoxyisochroman*-3-*one* (**2**)

A solution of ethyl chloroformate (7.4 ml) in benzene (10 ml) was added to a stirred solution of **1** (1.01 g) in benzene (30 ml), containing sodium bicarbonate (3 g). Stirring was continued for 1 hr, the reaction mixture filtered and the filtrate concentrated under reduced pressure to give the chloro compound as a thick liquid, which was dissolved in dimethylformamide (4.5 ml). To this potassium cyanide (1 g) was added, stirred at room temperature for 6 hr, water (50 ml) added and extracted with ether (3 × 50 ml). The ether layer was washed with water, dried (Na_2SO_4) and evaporated to give the cyano compound as a thick liquid which was dissolved in methanol (15 ml). To this was added a methanolic solution of KOH (0.75 g of KOH in 5 ml water and diluted to 7.5 ml with methanol) refluxed on a water-bath for 6-8 hr (monitored by TLC). Methanol was removed under reduced pressure, water (30 ml) added to the residue, and washed with ether. The aqueous layer was acidified with 1:1 HCl, extracted with ether (3 × 50 ml), the ether layer dried (Na_2SO_4) and evaporated to give a crude product. It was chromatographed over silica gel using pet. ether-ethyl acetate (9:1) as eluent to get a solid, which recrystallised from pet ether to furnish **2** (0.38 g, 39%), m.p. 74° (lit.[6,7] m.p. 76°); IR: 1730 (lactone carbonyl); PMR: 3.60 (*s*, 2H, Ar$-CH_2-$CO), 3.77 (*s*, 3H, OMe), 5.21 (*s*, 2H, Ar$-CH_2$O), 6.72 (*d*, J =2 Hz, 1H, C_8-H), 6.80 (*dd*, J=8 and 2 Hz, 1H, C_6 −H), 7.08 (*d*, J=8 Hz, 1H, C_5-H) (Found: C, 67.6; H, 5.7. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%).

N-[2-(3,4-*Dimethoxyphenyl*)*ethyl*]-(4-*methoxy*-2-*hydroxymethyl*)*phenylacetamide* (**4a**)

A solution of **2** (0.10 g) and homoveratrylamine (**3a**, 0.130 g) in absolute ethanol (5 ml) was stirred at room temperature for 24 hr (monitored by TLC). Ethanol was removed under reduced pressure, dry ether (5 ml) added to the gummy residue and scratched to get a powdery product, which was filtered and recrystallised from chloroform-pet. ether to give **4a** (0.160 g, 79%), m.p. 100°; IR: 3300 (OH/NH), 1650 (amide carbonyl), PMR: 2.56 (*t*, J=7 Hz, 2H, Ar$-CH_2-CH_2-$N), 3.26 (*t*, ill-resolved, J=7 Hz, 2H, Ar$-CH_2-CH_2-$N), 3.38 (*s*, 2H, $-COCH_2-$), 3.68 (*s*, 6H, 3 × OMe), 3.72 (*s*, 3H, OMe), 3.80 (*bs*, exchangeable with D_2O, OH/NH), 4.42 (*s*, 2H, Ar$-CH_2-$O), 6.32-7.05 (*m*, 5H, Ar−H) (Found: C, 66.7; H, 7.0. $C_{20}H_{25}NO_5$ requires C, 66.8; H, 7.0%).

N-[2-(3,4-*Methylenedioxyphenyl*)*ethyl*]-(4-*methoxy*-2-*hydroxymethyl*)*phenylacetamide* (**4b**)

It was obtained in 83% yield (0.16 g) as above by stirring at room temperature a solution of **2** (0.1 g) and homopiperonylamine (**3b**, 0.120 g) in absolute ethanol

(5 ml) for 24 hr; m.p. 126°; IR: 3240-3075 (OH/NH), 1650 (amide carbonyl); PMR: 2.65 (*t*, $J=7$ Hz, 2H, Ar $-CH_2-CH_2-N$), 3.38 (*t*, $J=7$ Hz, 2H, Ar$-CH_2$ $-CH_2-N$), 3.50 (*s*, 2H, $-COCH_2-$), 3.70 (*bs*, 1H, exchangeable with D_2O, OH/NH), 3.80 (*s*, 3H, OMe), 4.50 (*s*, 2H, Ar$-CH_2-O$), 5.91 (*s*, 2H, $-OCH_2O-$), 6.15 (*bs*, 1H, exchangeable with D_2O, OH/NH), 6.40-7.15 (*m*, 5H, Ar$-$H) (Found: C, 66.6; H, 5.9. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2%).

2,3,10-*Trimethoxy*-5,8,13,13*a*-*tetrahydro*-6*H*-*dibenzo*[*a*,*g*]*quinolizine* (**5a**)

PCl_5 (0.200 g) was added to a cooled (0°) solution of **4a** (0.100 g) in chloroform (10 ml) with stirring and the reaction mixture stirred further at room temperature for 4 hr. Chloroform was removed under reduced pressure, crushed ice added to the residue, washed with ether and the aqueous layer extracted with chloroform (2×25 ml). The chloroform layer was dried (Na_2SO_4) and solvent removed under reduced pressure to give an oily product. It was dissolved in methanol (10 ml) and sodium borohydride (0.3 g) added to this solution with stirring, in lots during 30 min. The reaction mixture was stirred at room temperature for 24 hr. Methanol was removed under reduced pressure, water (20 ml) added to the residue and extracted with ether (2×25 ml). The ether layer on drying (Na_2SO_4) and evaporation gave a crude product, which was chromatographed over silica gel. Elution with pet ether-ethyl acetate (9:1) gave a solid which on crystallisation from dichloromethane-pet. ether furnished **5a** (0.03 g, 33%), m.p. 113°; IR: 2750, 2700, 1630, 1510; UV: 279.8 (log ε 3.87), 232 nm (4.09); PMR: 2.40-4.05 (*m*, 9H, methylene and methine protons), 3.75, 3.83 and 3.86 (*s*, 3H each, $3\times$OMe), 6.52-7.08 (*m*, 5H, Ar$-$H), MS: *m/z* 325 (M^+), 310, 191, 190, 176, 164, 134, (Found: C, 73.8; H, 7.2. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1%).

2,3-*Methylenedioxy*-10-*methoxy*-5,8,13,13*a*-*tetrahydro*-6*H*-*dibenzo*[*a*,*g*]*quinolizine* (**5b**)

The amide (**4b**, 0.1 g) in chloroform (5 ml), on similar reaction with PCl_5 (0.20 g) furnished after work-up a solid which was dissolved in methanol (10 ml) and to this solution was added sodium borohydride (0.20 g) in lots during 30 min. It was stirred at room temperature for 3 hr and usual work-up as in the case of **5a** gave a crude product, which recrystallised from chloroform-pet. ether to give **5b** (0.03 g, 36%), m.p. 143°; IR: 2760, 2700, 2660, 1640, 1510; UV: 286.5 (log ε 3.94), 208 nm (4.46); PMR: 2.5-3.7 (*m*, 8H, methylene, methine protons and C_8-H), 3.78 (*s*, 3H, OMe), 4.00 (*d*, $J=15$ Hz, 1H, C_8-H), 5.89 (*s*, 2H, $-OCH_2O-$), 6.50-7.12 (*m*, 5H, Ar$-$H); MS: *m/z* 309 (M^+), 294, 175, 174, 161, 134 (Found: C, 74.0; H, 6.0. $C_{19}H_{19}O_3N$ requires C, 73.8; H, 6.2%).

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Aromatic Benzylation: Part V—Synthesis of Nuclear Benzylated Chalcones & Dihydrochalcones from Gallacetophenone & β-Resacetophenone as Analogues of Uvaretin & Isouvaretin

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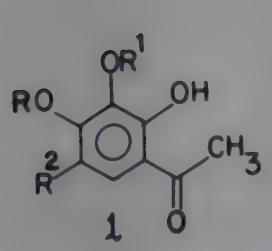
5-C-Benzylgallacetophenone (**1b**) has been prepared in two ways: (i) by treating gallacetophenone (**1a**) with benzyl alcohol in the presence of BF_3-Et_2O and (ii) by the Claisen rearrangement of 3,4-di-O-benzylgallacetophenone (**1d**) in TFA at room temperature. Partial O-benzylation of **1b** followed by chalcone condensation of the resulting ketone (**1e**) and catalytic hydrogenation of the resulting chalcone (**2e**) affords 5′-C-benzyl-2′,3′,4′-trihydroxydihydrochalcone (**3b**) as an analogue of isouvaretin. Similar series of reactions with partial methyl ether of **1b** give the dihydrochalcone (**3c**). Aromatic benzylation of resacetophenone by alkali method provides a complex mixture of O- and C-benzylated ketones (**4f**, **4d**, **4b**, **4g** and **4h**). Three of them (**4g**, **4b** and **4h**) have been converted into the corresponding C-benzylated 2′,4′-dihydroxydihydrochalcones (**6g**, **6b** and **6h**) as in the case of **1b**. Their partial methyl ethers (**6i**, **6k** and **6l**) have been synthesised similarly from **4i** **4k** and **4l**, respectively.

In continuation of our programme on the synthesis of nuclear benzylated chalcones and dihydrochalcones as analogues of biologically active uvaretin and isouvaretin[1-3], nuclear benzylated gallacetophenone and resacetophenone and their corresponding chalcones and dihydrochalcones have now been synthesised.

Aromatic benzylation of gallacetophenone (**1a**) was carried out in two ways: (i) reaction with benzyl alcohol in the presence of boron trifluoride etherate and dioxan; and (ii) Claisen migration of its dibenzyl ether (**1d**). Both gave only one product, identified as 5-C-benzylgallacetophenone (**1b**) through the preparation of its dimethyl ether (**1c**) which still possessed a chelated hydroxyl group (δ 12.17). The entry of one C-benzyl group was indicated by PMR spectra of **1b** and its dimethyl ether (**1c**) which exhibited only one aromatic proton (δ 7.10). The ketone **1b** on partial dibenzylation and subsequent condensation of **1e** with benzaldehyde in the presence of alkali and a small amount of dimethyl sulphoxide yielded 5′-C-benzyl-3′,4′-dibenzyloxy-2′-hydroxychalcone (**2e**) as shown by its UV and PMR spectra (see experimental). Hydrogenation of **2e** in the presence of Pd-C not only brought about debenzylation of the ether but also reduced the olefinic bond to afford 5′-*C*-benzyl-2′,3′,4′-trihydroxydihydrochalcone (**3b**). Its structure was established by its PMR spectrum which showed one singlet due to chelated −OH at δ 12.92 and a multiplet due to two methylene groups at δ 3.00-3.10. Further, it gave dimethyl ether (**3c**) which could also be synthesised from 5-*C*-benzyl-3,4-dimethoxy-2-hydroxyacetophenone (**1c**) by condensation with benzaldehyde in the presence of alkali followed by catalytic hydrogenation of the resulting chalcone (**2c**) in the presence of Pd-C.

Aromatic benzylation of β-resacetophenone (**4a**) was studied using benzyl bromide in the presence of methanolic potash at room temperature. Here, the product was found to be a complex mixture of five compounds which could be separated by column and preparative chromatography. Among them, three compounds 3-C-benzyl-(**4g**)-5-*C*-benzyl-(**4b**)- and 3,5-di-*C*-benzyl-(**4h**)-resacetophenones could easily be identified by direct comparison with the samples prepared earlier[1]. The fourth product was identified as 4-O-benzylresacetophenone (**4f**)[7] and the last one as 3-C-benzyl-4-benzyloxy-2-hydroxyacetophenone (**4d**) on the basis of its PMR spectrum which exhibited two *ortho*-coupled doublets due to two aromatic protons in positions 5 and 6 at δ 6.35 and 7.34 respectively. Further, there were signals due to the protons of one C-benzyl group and one O-benzyl group besides those due to a chelated −OH proton (δ 13.00) and acetyl protons (δ 2.48). The identity of **4d** was finally established by comparison with a synthetic sample prepared by partial O-benzylation of 3-C-benzylresacetophenone (**4g**) with one mol of benzyl chloride in acetone and anhyd. K_2CO_3.

A similar series of reactions with **4d**, **4j** and **4e** as with **1b** afforded chalcones (**5d**, **5j** and **5e** respectively) and dihydrochalcones (**6g**, **6b** and **6h** respectively). Their partial methyl ethers (**6i**, **6k** and **6l**) were also synthesised from **4i**, **4k** and **4l** respectively by similar steps of chalcone condensation and hydrogenation of the resulting chalcones (**5i**, **5k** and **5l** respectively).



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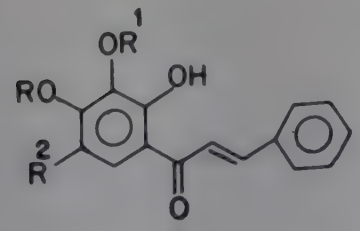

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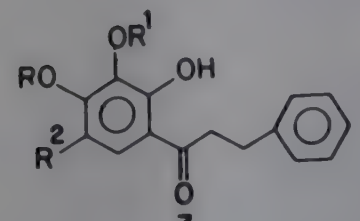

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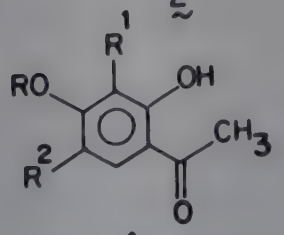

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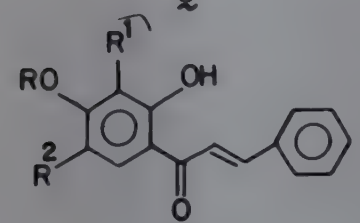

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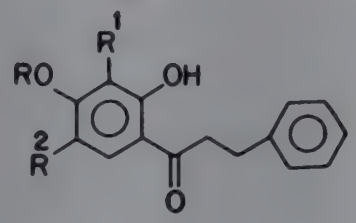
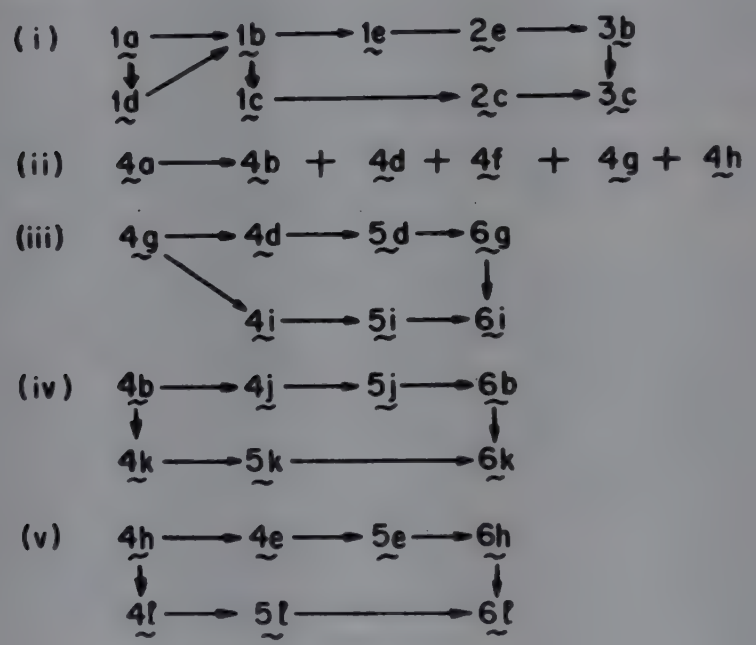


6

For formulae 1–6

	R	R^1	R^2
a.	H	H	H
b.	H	H	CH_2Ph
c.	CH_3	CH_3	CH_2Ph
d.	CH_2Ph	CH_2Ph	H
e.	CH_2Ph	CH_2Ph	CH_2Ph
f.	CH_2Ph	H	H
g.	H	CH_2Ph	H
h.	H.	CH_2Ph	CH_2Ph
i.	CH_3	CH_2Ph	H
j.	CH_2Ph	H	CH_2Ph
k.	CH_3	H	CH_2Ph
l.	CH_3	CH_2Ph	CH_2Ph

Schemes.



Experimental Procedure

Unless stated otherwise, all m.ps are uncorrected; pet. ether used had a boiling range 60-80°; silica gel was used for column chromatography and TLC; solvent systems used for TLC were: (A) benzene-pet. ether (8:2), (B) benzene, (C) benzene-ethyl acetate (19:1) and a drop of acetic acid; R_f values refer to TLC; UV data were recorded in methanol on a Perkin-Elmer UV model-554 spectrophotometer (λ_{max} in nm and figures in parentheses refer to log ε); IR spectra were recorded in KBr on a Perkin-Elmer infrared model 599-B spectrophotometer (ν_{max} in cm^{-1}); PMR spectra were recorded in $CDCl_3$ on Perkin-Elmer NMR model R-32 (90 MHz) and JEOL FT model JNM-FX-200 (200 MHz) instruments (chemical shifts in δ, ppm).

5-C-Benzylgallacetophenone (**1b**)

Method (*i*)—To a solution of gallacetophenone[4] (**1a**; 5.04 g, 30 mmol) in dry dioxan (100 ml) was added a solution of freshly distilled benzyl alcohol (3.5 ml, 32.4 mmol) in dioxan (20 ml) followed by a solution of BF_3-Et_2O (32 ml) in dioxan (10 ml). The resulting mixture was stirred and heated at 60-70° for 8 hr, cooled and diluted with ether. The ethereal layer gave a residue which on column chromatography and crystallization from chloroform furnished 5-C-benzyl-2,3,4-trihydroxyacetophenone (**1b**) as cream-coloured needles (3.8 g), m.p. 127-28°; gave green ferric reaction; R_f 0.35 (solvent C) (Found: C, 70.0; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%); UV: 226 (4.6) and 301 (4.1); IR: 3480 (br), 1620, 1590 and 1550; 90 MHz PMR: 2.42

(*s*, 3H, $-COCH_3$), 3.90 (*s*, 2H, $-CH_2Ph$), 7.00 (*s*, 1H, C_6-H), 7.15 (*s*, 5H, $-C_6H_5$), and 12.75 (*s*, 1H, chelated $-OH$).

Method (*ii*)—A solution of the ketone[5] **1d** (1.5 g, 5.8 mmol) in TFA (17.5 ml) was allowed to stand at room temperature for 70 hr, diluted with water and extracted with ether. The ethereal layer was worked-up and chromatographed as above. Fraction-A yielded **1b** (600 mg).

Reaction of 2,4-*dihydroxyacetophenone* (**4a**) *with benzyl bromide*

2,4-Dihydroxyacetophenone[6] (**4a**; 7.5 g, 49.3 mmol) was added to a well-cooled solution of KOH (10.5 g) in abs. CH_3OH (50 ml) and the resulting solution treated with benzyl bromide (9.2 g, 53.8 mmol) slowly with shaking. After keeping the reaction mixture for 24 hr at room temperature, it was diluted with ice-cold water, acidified and extracted with ether. The ethereal layer was dried over Na_2SO_4, evaporated to dryness and the residue subjected to column chromatography. Successive elution with (i) pet. ether, (ii) pet. ether-benzene (19:1), (iii) pet. ether-benzene (9:1), (iv) pet. ether-benzene (8:2), (v) pet. ether-benzene (3:1), and (vi) pet. ether-benzene (1:1) gave six fractions (A-F).

Fraction-A—It contained two compounds and was therefore subjected to preparative TLC using solvent-A. Elution with acetone and subsequent evaporation yielded a solid which crystallized from methanol to afford 3-C-benzyl-4-benzyloxy-2-hydroxyacetophenone (**4d**) as white crystals (25 mg), m.p. 118-20°; gave a violet green ferric reaction; R_f 0.52 (solvent B) (Found: C, 79.6; H, 6.1. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%); UV: 220 (3.9) and 270 (3.8); IR: 2965, 1625, 1570 and 1540; 90 MHz PMR: 2.48 (*s*, 3H, $-COCH_3$), 4.00 (*s*, 2H, $-CH_2Ph$), 5.01 (*s*, 2H, $-O-CH_2Ph$), 6.35 (*d*, J = 9.5 Hz, 1H, C_5-H), 7.10-7.20 (*s*, 10H, $2\times -C_6H_5$), 7.43 (*d*, J=9.5 Hz, 1H, C_6-H), and 13.00 (*s*, 1H, chelated $-OH$).

Fraction-B—It crystallized from benzene to yield 4-benzyloxy-2-hydroxyacetophenone (**4f**; 1.2 g), m.p. and m.m.p. 109-10° (lit.[7], m.p. 110°).

Fraction-C—It crystallized from benzene-pet. ether to afford 3,5-di-C-benzyl-2,4-dihydroxyacetophenone (**4h**; 250 mg), m.p. and m.m.p. 159-60° (lit.[1], m.p. 157-58°).

Fraction-D—It crystallized from benzene to furnish 3-C-benzyl-2,4-dihydroxyacetophenone (**4g**; 2.1 g), m.p. and m.m.p. 196-98° (lit.[1], m.p. 195-96°).

Fraction-E—It crystallized from benzene-pet. ether to give 5-C-benzyl-2,4-dihydroxyacetophenone (**4b**; 150 mg), m.p. and m.m.p. 140-42° (lit.[1], m.p. 140-41°).

Fraction-F—It crystallized from methanol to give β-resacetophenone (**4a**; 400 mg), m.p. and m.m.p. 142-43° (lit.[6], m.p. 142-43°).

Partial O-benzylation of **1b**, **4h** *and* **4b**

To a solution of the ketone (250 mg, 0.96 mmol) in dry acetone (25 ml) were added benzyl chloride [0.25 ml (1.92 mmol in the case of **1b**) and 0.12 ml in other cases], K_2CO_3 and KI. The mixture was refluxed for 90 min and the product crystallized from methanol or benzene. Following compounds were obtained.

5-C-Benzyl-2-hydroxy-3,4-dibenzyloxyacetophenone (**1e**) from **1b**: Colourless needles (270 mg), m.p. 56-58°; gave violet ferric reaction; R_f 0.61 (solvent B) (Found: C, 79.6; H, 6.1. $C_{29}H_{26}O_4$ requires C, 79.4; H, 6.1%); UV: 217 (4.9) and 280 (4.2); IR: 2970, 1615 and 1590; 90 MHz PMR: 2.47 (*s*, 3H, $COCH_3$), 3.84 (*s*, 2H, CH_2Ph), 5.10, 5.15 (2*s*, 2H each, $2\times -CH_2Ph$), 7.15 (*s*, 1H, C_6-H), 7.20-7.35 (*m*, 15H, $3\times -C_6H_5$), and 12.65 (*s*, 1H, chelated $-OH$).

3,5-Di-C-benzyl-4-benzyloxy-2-hydroxyacetophenone (**4e**) from **4h**: m.p. 87-89°; gave violet green ferric reaction; R_f 0.55 (solvent B) (Found: C, 82.2; H, 6.4. $C_{29}H_{26}O_3$ requires C, 82.4; H, 6.2%); UV: 229 (4.7) and 276 (3.7); IR: 2940, 1635, 1600 and 1595; 90 MHz PMR: (CCl_4): 2.53 (*s*, 3H, $-COCH_3$), 3.83, 3.98 (2*s*, 2H each, $2\times -CH_2Ph$), 4.50 (*s*, 2H, $-OCH_2Ph$), 7.05-7.23 (br *m*, 15H, $3\times -C_6H_5$), 7.45 (*s*, 1H, C_6-H) and 13.00 (*s*, 1H, chelated $-OH$).

5-C-Benzyl-4-benzyloxy-2-hydroxyacetophenone (**4j**) from **4b**: m.p. 100-102°; gave violet green ferric reaction; R_f 0.54 (solvent B) (Found: C, 79.3; H, 6.1. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%); UV: 229 (4.4) and 280 (4.0); 90 MHz PMR: 2.45 (*s*, 3H, $-COCH_3$), 4.03 (*s*, 2H, $-CH_2Ph$), 5.07 (*s*, 2H, $-O-CH_2Ph$), 6.53 (*s*, 1H, C_3-H), 7.23-7.42 (br *m*, 11H, $2\times -C_6H_5$ and C_6-H), and 12.67 (*s*, 1H, chelated $-OH$).

Chalcone condensation of **1e**, **4e**, **4d** *and* **4j**

To a solution of the ketone (0.59 mmol) in ethanol (10 ml) was added dimethyl sulphoxide dropwise until it was homogeneous, followed by benzaldehyde (0.06 ml) and KOH (0.55 g/15 ml). The product on column chromatography gave **2e**, **5e**, **5d** or **5j**. Their characterization data are as follows:

5′-C-Benzyl-2′-hydroxy-3′,4′-dibenzyloxychalcone (**2e**): Crystallized from ethanol as bright orange needles (220 mg), m.p. 99-100°; gave brown ferric reaction; R_f 0.65 (solvent B) (Found: C, 82.3; H, 5.4. $C_{36}H_{30}O_4$ requires C, 82.1; H, 5.7%); UV: 210 (4.6), 260 (4.2) and 337 (4.5); IR: 2950, 1650, 1610, and 1590; 200 MHz PMR: 3.90 (*s*, 2H, $-CH_2Ph$), 5.10, 5.15 (2*s*, 2H each, $2\times -O-CH_2Ph$), 7.24 (*s*, 21H, $4\times C_6H_5$ and C_6-H), 7.42 (*d*, J=17.0 Hz, 1H, $C_\alpha-H$), 7.87 (*d*, J=17.0 Hz, 1H, $C_\beta-H$), and 13.30 (*s*, 1H, chelated $-OH$).

3′,5′-Di-C-benzyl-4′-benzyloxy-2′-hydroxychalcone (**5e**): Crystallized from pet. ether as bright yellow needles (90 mg), m.p. 113-15°; gave brown ferric reaction; R_f 0.78 (solvent B) (Found: C, 84.5; H, 6.2.

$C_{36}H_{30}O_3$ requires C, 84.7; H, 5.9%); UV: 220 (5.0), 254 (4.7) and 326 (4.9); IR: 2990, 1640, 1610 and 1570; 90 MHz PMR: 3.95, 4.07 (2*s*, 2H each, 2 × $-CH_2Ph$), 4.57 (*s*, 2H, $-OCH_2Ph$), 7.12-7.20 (*m*, 20H, 4 × $-C_6H_5$), 7.40 (*d*, J = 17.0 Hz, 1H, $C_\alpha-H$), 7.49 (*s*, 1H, $C_{6'}-H$), 7.79 (*d*, J = 17 Hz, 1H, $C_\beta-H$), and 13.27 (*s*, 1H, chelated $-OH$).

3′-C-Benzyl-4′-benzyloxy-2′-hydroxychalcone (**5d**): Crystallized from ethanol as a yellow solid (300 mg), m.p. 135-36°; gave brown ferric reaction; R_f 0.66 (solvent B) (Found: C, 82.2; H, 6.3. $C_{29}H_{24}O_3$ requires C, 82.8; H, 5.8%); UV: 210 (4.7), 268 (4.2) and 334 (4.4); IR: 2990, 1625, 1610 and 1570; 90 MHz PMR: 4.03 (*s*, 2H, $-CH_2Ph$), 5.14 (*s*, 2H, $-OCH_2Ph$), 6.47 (*d*, J = 9.5 Hz, 1H, $C_{5'}-H$), 7.25 (*s*, 15H, 3 × $-C_6H_5$), 7.47 (*d*, J = 17.0 Hz, 1H, $C_\alpha-H$), 7.61 (*d*, J = 95 Hz, 1H, $C_{6'}-H$), 7.65 (*d*, J = 17.0 Hz, 1H, $C_\beta-H$), and 13.40 (*s*, 1H, chelated $-OH$).

5′-C-Benzyl-4′-benzyloxy-2′-hydroxychalcone (**5j**): Crystallized from CH_3OH as bright yellow needles (90 mg), m.p. 107-09°; gave brown ferric reaction; R_f 0.60 (solvent B) (Found: C, 82.5; H, 5.5. $C_{29}H_{24}O_3$ requires C, 82.8; H, 5.8%); UV: 210 (4.7), 268 (4.2) and 334 (4.4); IR: 2990, 1630, 1600 and 1585; 90 MHz PMR: 3.98 (*s*, 2H, $-CH_2Ph$), 5.06 (*s*, 2H, $-OCH_2Ph$), 6.52 (*s*, 1H, $C_{3'}-H$), 7.20-7.30 (*bm*, 15H, 3 × $-C_6H_5$), 7.35 (*d*, J = 17.0 Hz, 1H, $C_\alpha-H$), 7.62 (*s*, 1H, $C_{6'}-H$), 7.84 (*d*, J = 17.0 Hz, 1H, $C_\beta-H$), and 13.10 (*s*, 1H, chelated $-OH$).

Catalytic reduction of chalcones **2e**, **5e**, **5d** *and* **5j**

A solution of the chalcone (50 mg) in ethyl acetate (15 ml) was treated with 10% Pd-C (20 mg) and saturated with hydrogen at room temperature and atmospheric pressure. The characterization data of the products thus obtained are as follows:

5′-C-Benzyl-2′,3′,4′-trihydroxydihydrochalcone (**3b**) from **2e**: Crystallized from benzene-pet. ether as cream coloured needles (25 mg), m.p. 95-96°; gave violet green ferric reaction; R_f 0.49 (solvent C) (Found: C, 75.5; H, 5.9. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%); UV: 216 (4.4) and 274 (4.1); IR: 3320, 2990, 1645, 1600 and 1575; 90 MHz PMR: 3.00-3.10 (*m*, 4H, $C_\alpha-2H$ and $C_\beta-2H$), 3.90 (*s*, 2H, $-CH_2Ph$), 7.05 (*s*, 1H, $C_{6'}-H$), 7.21 (*s*, 10H, 2 × $-C_6H_5$), and 12.92 (*s*, 1H, chelated $-OH$).

3′,5′-Di-C-benzyl-2′,4′-dihydroxydihydrochalcone (**6h**) from **5e**: Crystallized from hot pet. ether as a cream coloured solid, m.p. 135-36°; gave green ferric reaction; R_f 0.48 (solvent B) (Found: C, 82.6; H, 6.5. $C_{29}H_{26}O_3$ requires C, 82.4; H, 6.2%); UV: 220 (4.9) and 282 (4.2); IR: 2985 (br), 1635, 1600, 1560 and 1530; 90 MHz PMR: 2.90-3.00 (*m*, 4H, $C_\alpha-2H$ and $C_\beta-2H$), 3.75-3.90 (2*s*, 2H each, 2 × $-CH_2Ph$), 7.03-7.15 (*m*, 15H, 3 × $-C_6H_5$), 7.31 (*s*, 1H, $C_{6'}-H$), and 12.83 (*s*, 1H, chelated $-OH$).

3′-C-Benzyl-2′,4′-dihydroxydihydrochalcone (**6g**) from **5d**: Crystallized from acetonitrile as colourless needles, m.p. 157-58°; gave green ferric reaction; R_f 0.30 (solvent B) (Found: C, 79.3; H, 5.8. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%); UV: 228 (4.9) and 269 (4.8); IR: 2980 (b), 1605, 1590, and 1550; 90 MHz PMR: 2.97-3.02 (*m*, 4H, $C_\alpha-2H$ and $C_\beta-2H$), 4.00 (*s*, 2H, $-CH_2Ph$), 5.01 (*s*, 1H, $-OH$, exchangeable with D_2O), 6.16 (*d*, J = 9.5 Hz, 1H, $C_{5'}-H$), 7.10 (*s*, 10H, 2 × $-C_6H_5$), 7.36 (*d*, J = 9.5 Hz, 1H, $C_{6'}-H$), and 13.20 (*s*, 1H, chelated $-OH$).

5′-C-Benzyl-2′,4′-dihydroxydihydrochalcone (**6b**) from **5j**: Crystallized from hot methanol as colourless crystals (15 mg), m.p. 110-12°; gave violet ferric reaction; R_f 0.32 (solvent C) (Found: C, 79.4; H, 6.2. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%); UV: 219 (4.7) and 280 (4.5); IR: 2985 (br), 1640, 1600 and 1545; 200 MHz PMR: 3.00 and 3.11 (2*t*, 2H each, $C_\alpha-2H$ and $C_\beta-2H$), 3.90 (*s*, 2H, $-CH_2Ph$), 6.54 (*s*, 1H, C_3-H), 7.16-7.29 (br *m*, 10H, 2 × $-C_6H_5$), 7.43 (*s*, 1H, $C_{6'}-H$), and 12.70 (*s*, 1H, chelated $-OH$).

5-C-Benzyl-2-hydroxy-3,4-dimethoxy-acetophenone (**1c**)

To a solution of **1b** (200 mg, 0.7 mmol) in dry acetone (20 ml) were added Me_2SO_4 (0.15 ml, 1.54 mmol) and freshly ignited K_2CO_3 (0.43 g; 3.10 mmol). The resulting mixture was refluxed for 50 min. The product crystallized from ethyl acetate-pet. ether to give **1c** as a colourless solid (150 mg), m.p. 42-43°; gave green ferric reaction; R_f 0.57 (solvent B) (Found: C, 71.5; H, 6.4. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%); UV: 228 (4.9) and 269 (4.6); IR: 2990, 1630, 1595 and 1550; 90 MHz PMR(CCl_4): 2.36 (*s*, 3H, $-COCH_3$), 3.72, 3.75 (2*s*, 3H each, 2 × $-OCH_3$), 3.78 (*s*, 2H, $-CH_2Ph$), 7.10 (*s*, 1H, C_6-H), 7.18-7.20 (*m*, 5H, $-C_6H_5$), and 12.17 (*s*, 1H, chelated $-OH$).

Chalcone condensation of **1c**, **4l**, **4i** *and* **4k**

To a solution of the ketone (150 mg, 0.58 mmol) in ethanol (20 ml) were added benzaldehyde (0.09 ml) and aq. KOH (0.5 g/10 ml) and the resulting mixture was refluxed on a water-bath for 20 min. After keeping the mixture at room temperature for 48 hr, it was diluted with H_2O (50 ml) and extracted with ether. The alkaline layer was acidified when an orange solid separated out. It was collected, macerated with aq. $NaHCO_3$ and finally subjected to column chromatography. The characterization data of the products thus obtained are as follows.

5′-C-Benzyl-2′-hydroxy-3′,4′-dimethoxychalcone (**2c**) from **1c**: Crystallized from benzene-pet. ether as yellow needles (80 mg), m.p. 82-83°; gave violet green ferric reaction; R_f 0.47 (solvent B) (Found: C, 76.9; H,

6.0. $C_{24}H_{22}O_4$ requires C, 77.0; H, 5.9%); UV: 216 (4.8), 268 (4.3) and 329 (4.6); IR: 2950, 1635, 1600, 1580 and 1520; 90 MHz PMR: 3.80, 3.84 (2*s*, 3H each, 2 × $-OCH_3$), 4.10 (*s*, 2H, $-CH_2Ph$), 7.02-7.10 (*s*, 11H, 2 × $-C_6H_5$ and $C_{6'}-H$), 7.40 (*d*, $J=17.0$ Hz, 1H, $C_\alpha-H$), 7.5 (*d*, $J=17.0$ Hz, 1H, $C_\beta-H$), and 12.12 (*s*, 1H, chelated $-OH$).

3′,5′-Di-C-benzyl-2′-hydroxy-4′-methoxychalcone (**5l**) from **4l**: Crystallized from methanol as bright yellow needles (40 mg), m.p. 104-05°; gave violet brown ferric reaction; R_f 0.76 (solvent B) (Found: C, 82.6; H, 6.2. $C_{30}H_{26}O_3$ requires C, 82.9; H, 6.0%); UV: 210 (4.7), 262 (3.9), and 326 (4.0); IR: 2950, 1610 and 1580; 200 MHz PMR: 3.58 (*s*, 3H, $-OCH_3$), 4.02, 4.06 (2*s*, 2H each, 2 × $-CH_2Ph$), 7.18-7.24 (br *m*, 15H, 3 × $-C_6H_5$), 7.42 (*s*, 1H, $C_{6'}-H$), 7.60 (*d*, $J=17.0$ Hz, 1H, $C_\alpha-H$), 7.80 (*d*, $J=17.0$ Hz, 1H, $C_\beta-H$), and 13.20 (*s*, 1H, chelated $-OH$).

3′-C-Benzyl-2′-hydroxy-4′-methoxychalcone (**5i**) from **4i**: Crystallized from chloroform as yellow needles (50 mg), m.p. 155-56°; gave brown ferric reaction; R_f 0.64 (solvent B) (Found: C, 80.0; H, 5.6. $C_{23}H_{20}O_3$ requires C, 80.2; H, 5.9%); UV: 208 (4.6), 270 (4.2) and 322 (4.3); IR: 2900, 1640, 1605 and 1560; 90 MHz PMR: 3.81 (*s*, 3H, $-OCH_3$), 4.01 (*s*, 2H, $-CH_2Ph$), 6.40 (*d*, $J=9.5$ Hz, 1H, $C_{5'}-H$), 7.19-7.39 (br *m*, 10H, 2 × $-C_6H_5$), 7.49 (*d*, $J=17.0$ Hz, 1H, $C_\alpha-H$), 7.61 (*d*, $J=9.5$ Hz, 1H, $C_{6'}-H$), 7.65 (*d*, $J=17.0$ Hz, 1H, $C_\beta-H$), and 12.32 (*s*, 1H, chelated $-OH$).

5′-*C*-Benzyl-2′-hydroxy-4′-methoxychalcone (**5k**) from **4k**: Crystallized from methanol as yellow needles (80 mg), m.p. 137-38°; gave brown ferric reaction; R_f 0.63 (solvent B) (Found: C, 80.1; H, 5.6. $C_{23}H_{20}O_3$ requires C, 80.2; H, 5.9%); UV: 220 (4.2), 256 (3.8) and 340 (4.1); IR: 2900, 1630, 1600 and 1570; 90 MHz PMR: 3.86 (*s*, 3H, $-OCH_3$), 3.94 (*s*, 2H, $-CH_2Ph$), 6.46 (*s*, 1H, $C_{3'}-H$), 7.20-7.30 (*bm*, 10H, 2 × $-C_6H_5$), 7.48 (*d*, $J=17.0$ Hz, 1H, $C_\alpha-H$), 7.51 (*s*, 1H, $C_{6'}-H$), 7.68 (*d*, $J=17.0$ Hz, 1H, $C_\beta-H$) and 13.40 (*s*, 1H, chelated $-OH$).

Partial O-methylated dihydrochalcones

Method (*i*)

A solution of the above chalcone (50 mg) in ethyl acetate (15 ml) was hydrogenated with 10% Pd-C (20 mg). The following products were obtained.

5′-C-Benzyl-2′-hydroxy-3′,4′-dimethoxydihydrochalcone (**3c**) from **2c**: Crystallized from pet. ether as white crystals (30 mg), m.p. 74-76°; gave green ferric reaction; R_f 0.60 (solvent B) (Found: C, 76.4; H, 6.5. $C_{24}H_{24}O_4$ requires C, 76.6; H, 6.4%); UV: 219 (4.9) and 280 (3.9); IR: 2950, 1635, 1585 and 1560; 90 MHz PMR: 2.95-3.10 (*m*, 4H, $C_\alpha-2H$ and $C_\beta-2H$), 3.84, 3.87 (2*s*, 3H each, 2 × $-OCH_3$), 3.94 (*s*, 2H, $-CH_2Ph$), 7.10-7.25 (*m*, 11H, 2 × $-C_6H_5$ and $C_{6'}-H$), and 12.60 (*s*, 1H, chelated $-OH$).

3′,5′-Di-C-benzyl-2′-hydroxy-4′-methoxydihydrochalcone (**6l**) from **5l**: Crystallized from benzene-pet. ether as white crystals, m.p. 70-72°; gave violet ferric reaction; R_f 0.53 (solvent B) (Found: C, 82.4; H, 6.7. $C_{30}H_{28}O_3$ requires C, 82.5; H, 6.5%); UV: 222 (4.0) and 270 (3.8); IR: 2950, 1630, 1595 and 1550; 200 MHz PMR: 2.88, 2.92 (2*t*, 2H each, $C_\alpha-2H$ and $C_\beta-2H$), 3.86, 3.87 (2*s*, 2H each, 2 × $-CH_2Ph$), 3.90 (*s*, 3H, $-OCH_3$), 7.20-7.40 (*m*, 15H, 3 × $-C_6H_5$), 7.42 (*s*, 1H, $C_{6'}-H$), and 12.80 (*s*, 1H, chelated $-OH$).

3′-C-Benzyl-2′-hydroxy-4′-methoxydihydrochalcone (**6i**) from **5i**: Crystallized from ether as light yellow needles, m.p. 114-16°; gave violet ferric reaction; R_f 0.52 (solvent B) (Found: C, 79.5; H, 6.1. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%); UV: 220 (4.5) and 280 (3.9); IR: 2915, 1630, 1600, 1565 and 1550; 90 MHz PMR: 3.02, 3.20 (2*t*, 2H each, $C_\alpha-2H$, and $C_\beta-2H$), 3.80 (*s*, 3H, $-OCH_3$), 3.91 (*s*, 2H, $-CH_2Ph$), 6.40 (*d*, $J=9.5$ Hz, 1H, $C_{5'}-H$), 7.20 (*m*, 10H, 2 × $-C_6H_5$), 7.60 (*d*, $J=9.5$ Hz, 1H, $C_{6'}-H$), and 12.82 (*s*, 1H, chelated $-OH$).

5′-C-Benzyl-2′-hydroxy-4′-methoxydihydrochalcone (**6k**) from **5k**: Crystallized from ethyl acetate-pet. ether as colourless solid (30 mg), m.p. 85-86°; gave violet ferric reaction; R_f 0.51 (solvent B) (Found: C, 79.5; H, 6.6. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%); UV: 212 (4.5) and 276 (4.1); IR: 2970, 1620, 1595 and 1500; 90 MHz PMR: 3.05-3.15 (*m*, 4H, $C_\alpha-2H$ and $C_\beta-2H$), 3.88 (*s*, 3H, $-OCH_3$), 3.95 (*s*, 2H, $-CH_2Ph$), 6.48 (*s*, 1H, $C_{3'}-H$), 7.22 (*s*, 10H, 2 × $-C_6H_5$), 7.44 (*s*, 1H, $C_{6'}-H$), and 13.02 (*s*, 1H, chelated $-OH$).

Method (*ii*)

The dihydrochalcones **3b**, **6h**, **6g** and **6b** were separately methylated partially with dimethyl sulphate, K_2CO_3 in dry acetone to give **3c**, **6l**, **6i** and **6k** respectively, identical with those obtained above.

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Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Part LI—Reaction of 2-Mercapto-3*H*-imidazo[4,5-*f*]quinoline with α,β-Bifunctional Compounds

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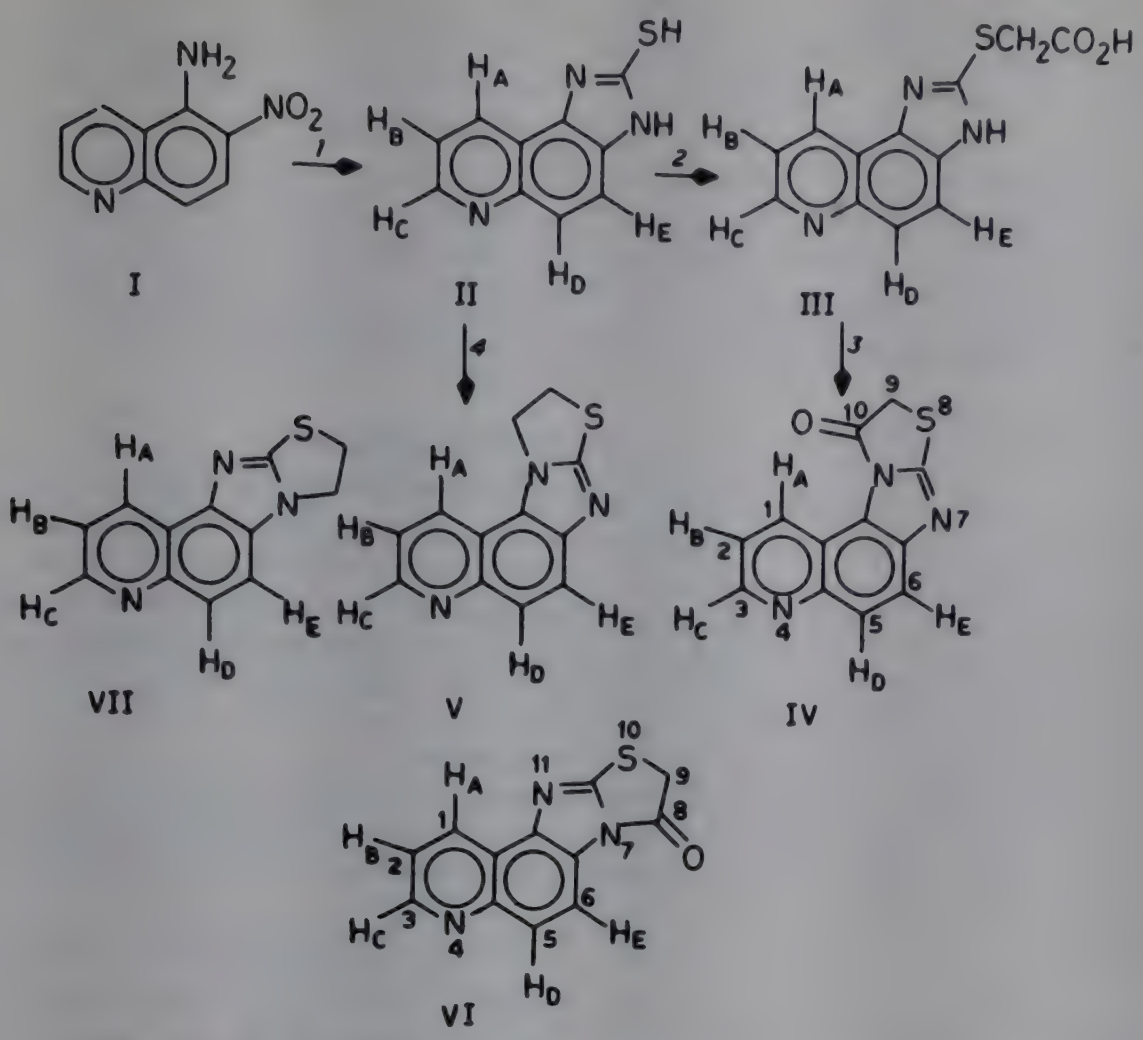
2-Mercapto-3*H*-imidazo [4,5-*f*] quinoline (II), obtained by the reduction of 5-amino-6-nitroaniline (I) followed by reaction of the diamine with carbon disulphide *in situ*, on reaction with chloroacetic acid gives 3*H*-imidazo [4,5-*f*] quinoline-2-thiolacetic acid (III). The acid III on cyclization with a mixture of acetic anhydride and pyridine furnishes thiazolo [3',2':1,2] imidazo [4,5-*f*] quinolin-10(9*H*)-one (IV) and not the other isomer thiazolo [3',2':1,2] imidazo [4,5-*f*] quinolin-8(9*H*)-one (VI), as revealed by PMR spectral data. Similarly, II on condensation with 1,2-dibromoethane gives 9,10-dihydrothiazolo-[3',2':1,2] imidazo [4,5-*f*] quinoline (V).

In continuation of our studies on the orientation of cyclization in the reaction of unsymmetrical triazinoindolthione[1], mercaptobenzimidazole[2], mercaptobenzotriazine[3], mercaptoquinazolone[4] and triazine-thione[5] with bifunctional compounds, we now wish to report the reaction of another heterocyclic system i.e., 2-mercapto-3*H*-imidazo [4,5-*f*] quinoline with chloroacetic acid and 1,2-dibromoethane furnishing the thiazolo [3',2':1,2] imidazo [4,5-*f*] quinoline system (Scheme 1). Literature survey reveals that the synthesis of only one compound of this series has been reported in a German patent[6] by heating 5, 6-dihalo-7, 8-quinoline-quinone with 2-amino-4-methylthiazole. However, no proof for the structure has been furnished.

5-Amino-6-nitroquinoline (I) on reduction with Raney nickel and hydrazine hydrate and subsequent reaction of the resulting diamine with carbon disulphide *in situ*, following the method of Van Allan and Deacon[7] for the synthesis of 2-mercaptobenzimidazole, afforded the desired starting material, 2-mercapto-3*H*-imidazo [4,5-*f*] quinoline (II). The compound II when reacted with chloroacetic acid gave 3*H*-imidazo [4,5-*f*] quinoline-2-thiolacetic acid (III). The acid III being unsymmetrical, on cyclization was expected to yield thiazolo [3',2':1,2] imidazo [4,5-*f*] quinolin-10(9*H*)-one (IV) or thiazolo [3',2':1,2] imidazo [4,5-*f*] quinolin-8(9*H*)one (VI) or both depending upon the mode of cyclization. The acid III, however, on treatment with a mixture of acetic anhydride and pyridine underwent cyclization furnishing a single product (TLC). The appearance of a band at 1735 cm^{-1} ($\geq N-CO-$) in the IR spectrum of the product suggested that the cyclization had indeed taken place. The exhibition of molecular ion peak at *m/z* 241 in the mass spectrum of the TLC-pure product further confirmed its cyclic nature. The structure thiazolo [3',2':1,2] imidazo [4,5-*f*] quinoline-10(9*H*)-one (IV) and not of the other isomer (VI) was assigned to the cyclization product on the basis of PMR spectral studies.

The reaction of II with 1,2-dibromoethane gave a single product (TLC) which may be represented either by structure 9, 10-dihydrothiazolo [3',2':1,2] imidazo [4,5-*f*] quinoline (V) or 8, 9-dihydrothiazolo [3',2':1,2] imidazo [4,5-*f*] quinoline (VII). In either structure (V or VII) the PMR signals at δ 9.61, 8.36, 9.34, 8.50 and 8.48 may be due to H_A, H_B, H_C, H_D and H_E protons respectively. Comparison of the chemical shifts of H_A in V (or VII) with that of H_A in the cyclization product obtained from the acid III supports the structure IV. In V (or VII), H_A has a value δ 9.61 and the signal at 10.62 (a value sufficiently higher than 9.61, the difference being 1.01, is due to the deshielding effect of the carbonyl group on the *peri*-proton H_A arising from the magnetic anisotropy of the carbonyl group) in the cyclization product, obtained from III is in conformity with the structure IV. Such a downfield signal for a *peri*-proton cannot be expected from VI. Had the structure VI been correct, the H_A, H_B, H_C and H_D protons would have resonated at about the same region as in V (or VII), and only H_E proton would have been deshielded due to carbonyl group by δ 0.45. This value has been obtained from thiazolo [3,2-*a*] benzimidazol-3-one in which the signals at δ 8.22, 7.62, 7.62 and 7.77 were assigned to the H_5, H_6, H_7 and H_8 protons respectively; 8.22-7.77 = 0.45 (ref. 8). In the cyclization product of III, H_E proton resonated at δ 8.56, almost the same region as in V (or VII).

The same conclusion was also arrived at from the



SCHEME 1

comparison of chemical shifts of the respective aromatic protons in the acid III and its cyclization product IV (or VI). In the acid III, the signals at δ 9.82, 8.45, 9.37, 8.70 and 8.59 were assigned to the H_A, H_B, H_C, H_D and H_E protons respectively. The signal at δ 10.62 (in place of 9.82 observed in the acid) in the cyclization product must be due to H_A as this proton is deshielded by carbonyl group, thus supporting the structure IV. In a similar way structure V was assigned to the product obtained from the reaction of II with 1,2-dibromoethane.

Experimental Procedure

Melting points reported are uncorrected. TLC was performed on silica gel G plates using benzene-acetone (3:1) as solvent. IR spectra were recorded in nujol mull on a Beckman IR-20 spectrophotometer (ν_{max} in cm^{-1}), PMR spectra in TFA on a Perkin-Elmer 90 MHz spectrometer using TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on a Perkin-Elmer-Hitachi RMU-6D or a Varian Mat 112 instrument as 70 eV.

5-Amino-6-nitroquinoline (I)

6-Nitroquinoline, obtained from *p*-nitroaniline by Skraup's synthesis, on reaction with hydroxylamine hydrochloride according to the method of Huisgen[9], furnished the desired compound in 90% yield, m.p. 272° (EtOH) (lit.[9], m.p. 272°).

2-Mercapto-3H-imidazo[4,5-f]quinoline (II)

It was prepared in 50% yield by the reduction of I with Raney nickel and hydrazine hydrate and subsequent reaction of the resulting diamine with carbon disulphide *in situ*, following the method of Van Allan and Deacon[7] for the synthesis of 2-mercaptobenzimidazole, m.p. >300° (EtOH-DMF) (Found: S, 15.9. $C_{10}H_7N_3S$ requires S, 15.9%); IR: 1580, 1605 (C=N, C=C); PMR: 8.30 (1H, *dd*, H_B, J_{BC} =7Hz, J_{AB}=9Hz), 8.38 (1H, *d*, H_1, J_{DE}=8Hz), 8.47 (1H, *d*, H_D, J_{DE}=8Hz), 9.23 (1H, *d*, H_C, J_{BC}=7Hz), 9.61 (1H, *d*, H_A, J_{AB}=9Hz).

3H-Imidazo-[4,5-f]quinoline-2-thiolacetic acid (III)

A mixture of II (2.01 g, 0.01 mol), chloroacetic acid (0.94 g, 0.01 mol) and potassium hydroxide (1.12 g) in ethanol (50 ml) was heated under reflux for 6 hr, filtered to remove insoluble impurities, diluted with water, acidified with dil. acetic acid and kept

overnight. The solid, thus separated, was filtered, washed well with water and crystallized from DMF to give III as pale yellow granules, m.p. >300°, yield 2 g (77%) (Found: S, 12.3. $C_{12}H_9N_3SO_2$ requires S, 12.4%); IR: 1570, 1600 (C=N, C=C), 1650 (C=O), 2660-2560 (−COOH), 3100 (NH); PMR: 4.45 (2H, *s*, CH_2), 8.45 (1H, *dd*, H_B, J_{BC}=7Hz, J_{AB}=9Hz), 8.59 (1H, *d*, H_E, J_{DE}=9Hz), 8.70 (1H, *d*, H_D, J_{DE}=9Hz), 9.37 (1H, *d*, H_C, J_{BC}=7Hz), 9.82 (1H, *d*, H_A, J_{AB}=9Hz).

Thiazolo[3′,2′:1,2]*imidazo*[4,5-*f*]*quinoline*-10(9*H*)-one (IV)

The acid III (1.0 g) in a mixture of acetic anhydride (1 ml) and pyridine (3 ml) was heated on a steam-bath for 15 min, kept overnight and the solid thus separated was filtered, washed well with water and finally crystallized from ethanol to give IV as fine cream coloured needles, m.p. 230°, yield 0.2 g (21%) (Found: S, 13.2. $C_{12}H_7N_3SO$ requires S, 13.3%); IR: 1570, 1600 (C=N, C=C), 1735 (C=O); PMR: 5.00 (2H, *s*, SCH_2), 8.33 (1H, *dd*, H_B, J_{BC}=7.5Hz, J_{AB}=9Hz), 8.56 (1H, *d*, H_E, J_{DE}=8Hz), 8.69 (1H, *d*, H_D, J_{DE}=8Hz), 9.36 (1H, *d*, H_C, J_{BC}=7.5Hz), 10.62 (1H, *d*, H_A, J_{AB}=9Hz); MS: *m/z* 241 [M^{+}·].

9,10-*Dihydrothiazolo*[3′,2′:1,2]*imidazo*-[4,5-*f*]*quinoline* (*V*)

A mixture of II (2.01 g, 0.01 mol) and 1,2-dibromoethane (1.88 g, 0.01 mol) in anhyd. ethanol (20 ml) and DMF (30 ml) was heated under reflux for 6 hr, cooled to room temperature and poured into water. The hydrobromide, thus separated, was neutralized with sodium carbonate to yield the free base V which was crystallized from DMF as brown needles, m.p. 260°, yield 1.0 g (44%) (Found: S, 14.0. $C_{12}H_9N_3S$ requires S, 14.1%); IR: 1580, 1630 (C=N, C=C); PMR: 4.58 (2H, *t*, SCH_2), 5.41 (2H, *t*, $\geq NCH_2$), 8.36 (1H, *dd*, H_B, J_{BC}=7Hz, J_{AB}=9Hz), 8.48 (1H, *d*, H_E, J_{DE}=9Hz), 8.50 (1H, *d*, H_D, J_{DE}=9Hz), 9.34 (1H, *d*, H_C, J_{BC}=7Hz), 9.61 (1H, *d*, H_A, J_{AB}=9Hz); MS: *m/z* 227 [M]$^{+}$

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Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Part LII—Synthesis of 6,7-Dimethoxy & 5,8-Dimethoxy Thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones, Thiazolo[3,2-*a*]benzimidazoles & 2,3-Dihydrothiazolo[3,2-*a*]benzimidazoles

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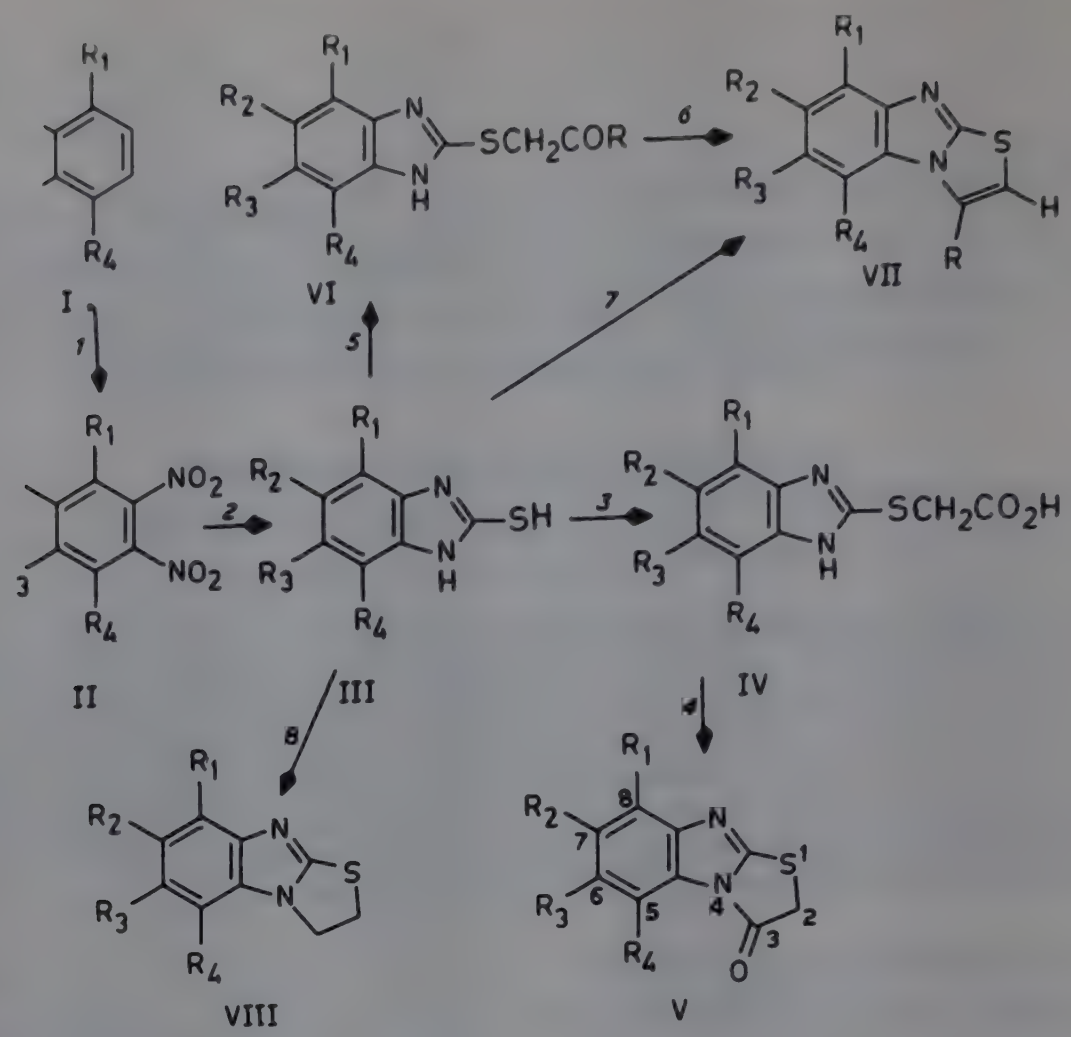
5,6-Dimethoxy- (IIIa) and 4,7-dimethoxy-2-mercaptobenzimidazoles (IIIb), obtained by the successive reactions involving nitration of dimethoxybenzenes (Ia,b), reduction of the *o*-dinitrobenzenes (IIa,b) with Raney nickel and hydrazine hydrate followed by treatment of the resulting diamines with carbon disulphide *in situ*, on reaction with chloroacetic acid give the corresponding acids (IVa,b) which on cyclization with a mixture of acetic anhydride and pyridine furnish 6,7-dimethoxy- and 5,8-dimethoxythiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (Va and Vb) respectively. Condensation of IIIa,b with α-halogenoketones and subsequent PPA-catalyzed cyclization of the resulting ketones (VIa,b) give 6,7-dimethoxy- and 5,8-dimethoxythiazolo[3,2-*a*]benzimidazoles (VIIa and VIIb) respectively. Similarly, the reaction of IIIa,b with 1,2-dibromoethane affords the corresponding dihydrothiazolo[3,2-*a*]benzimidazoles (VIIIa,b).

In furtherene of our interest in the synthesis of thiazolo-benzimidazoles[1] as potent fungicides and bactericides we now wish to report the synthesis of dimethoxythiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (Va,b), dimethoxythiazolo[3,2-*a*]benzimidazoles (VIIa,b) and dihydrodimethoxythiazolo[3,2-*a*]-benzimidazoles (VIIIa,b) starting from dimethoxy-2-mercaptobenzimidazoles (IIIa,b) (Scheme 1).

4,5-Dinitroveratrol (IIa) and 3,6-dimethoxy-1,2-nitrobenzene (IIb), obtained by the nitration of Ia,b, on reduction with Raney nickel and hydrazine hydrate and subsequent treatment of the resulting diamines with carbon disulphide *in situ* furnished 5,6-dimethoxy- and 4,7-dimethoxy-2-mercapto-benzimidazoles (IIIa and IIIb) respectively. Mercaptob-enzimidazoles (IIIa,b) when condensed with ch-loroacetic acids gave the acids IVa,b which on treatment with a mixture of acetic anhydride and pyridine underwent cyclization to give 6,7-dimetho-xy- and 5,8-dimethoxythiazolo[3,2-*a*]-benzimidazol-3(2*H*)-ones (Va and Vb) respectively. The structural assignments of V were based on IR, PMR and mass spectral data. The appearance of bands at 1730 ($\geq N-CO-$) and 1750 cm^{-1} ($\geq N-CO-$) in the IR spectra of Va and Vb corroborated that cyclization had indeed taken place. Appearance of molecular ion peaks at *m/z* 250 (100 %) and 250 (100 %) in the mass spectra of Va and Vb was compatible with the assigned structures.

Mercaptobenzimidazoles (IIIa,b) on condensation with α-halogenoketones yielded the ketones VIa,b which on treatment with polyphosphoric acid underwent cyclization giving 6,7-dimethoxy- and 5,8-dimethoxy-3-arylthiazolo[3,2-*a*]benzimidazoles (VIIa and VIIb) respectively. The structures of the ketones (VIa,b) and the thiazoles (VIIa,b) were supported by their IR spectral data. The ketones VIa,b absorbed in the region 1670-1700 cm^{-1} (C = O) and the absence of this band in the IR spectra of VIIa,b showed the absence of the carbonyl group suggesting thereby the cyclic structure for VII. The thiazole structure (VII) was further supported by PMR and mass spectral data. The signals appearing at δ 6.74 (1 H, *s*, C_2-H), 6.99 (1 H, broad *s*, C_2-H) and 7.19 (1 H, *s*, C_2-H) in the PMR spectra of VIIa (R = *p*-$O_2NC_6H_4$), VIIa (R = CH_3) and VIIb (R = *p*-BrC_6H_4) and exhibition of molecular ion peak at *m/z* 355 (100 %) and isotopic cluster molecular ion peak at *m/z* 388/390 in the ratio of 1 : 1 in the mass spectra of VIIa (R = *p*-$O_2NC_6H_4$) and VIIIb (R = *p*-BrC_6H_4) respectively corroborated the cyclic structure of VII. The reaction of IIIa with chloroacetone, however, furnished directly the cyclization product VIIa (R = CH_3).

Similarly, the condensation of IIIa,b with 1,2-dibromoethane yielded 6,7-dimethoxy- and 5,8-dimethoxy-2,3-dihydrothiazolo[3,2-*a*]benzimidazoles (VIIIa and VIIIb) respectively in one step. The structures VIIIa,b were also supported by their PMR and mass spectral data. The molecular ion peaks of VIIIa and VIIIb at *m/z* 236 (100 %) and 236 (52 %) respectively were compatible with their assigned structures.



a, $R_1 = R_4 = H$, $R_2 = R_3 = OCH_3$
b, $R_1 = R_4 = OCH_3$, $R_2 = R_3 = H$
c $R_1 = R_2 = R_4 = H$, $R_3 = OCH_3$
d, $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$
e, $R_1 = R_2 = R_3 = R_4 = H$

1. Ac_2O, Conc. HNO_3 ; 2. (i) Raney nickel, H_2NNH_2, H_2O ; (ii) CS_2, KOH ;
3. $ClCH_2CO_2H$, KOH ; 4. Ac_2O, pyridine ; 5. $RCOCH_2Br$; 6. PPA ;
7. CH_3COCH_2Cl ; 8. $BrCH_2CH_2Br$.

SCHEME 1

In an earlier study[2], we brought about cyclization of the acid IVc and obtained a single product to which the structure Vc and not the isomeric structure Vd was assigned by comparing the observed and calculated chemical shifts for the aromatic protons of the cyclization product Vc or Vd. The calculated chemical shifts were derived from Ve which was used as a reference compound. It was thought of interest to ascertain whether Va could be used as a reference compound for the confirmation of the structure Vc.

The assignments of the PMR signals for C_5-H and C_8-H protons in Vc and Vd were derived from the calculations by taking into consideration the shielding effect of methoxy group (δ 0.43 for *ortho*-proton and 0.09 for *meta*-proton)[3] on the chemical shifts for the corresponding protons of Va. In the PMR spectrum of Va in DMSO-d_6, the signals at δ 7.33 and 7.15 were assigned for C_5-H and C_8-H protons respectively.

If structure Vc is correct for the cyclization product obtained from IVc ($\equiv$IVd), the calculated chemical shifts for C_5-H and C_8-H protons would be δ 7.42 (7.33 + 0.09) and 7.58 (7.15 + 0.43) respectively (Set-A). On the other hand, if structure Vd is correct for the cyclization product obtained from IVc ($\equiv$IVd), the calculated chemical shifts for C_5-H and C_8-H protons would be δ 7.76 (7.33 + 0.43) and 7.24 (7.15 + 0.09) respectively (Set-B).

The observed signals in the spectrum of the cyclization product at δ 7.47 and 7.57 (Set-C) may be due to C_5-H and C_8-H protons respectively if structure Vc is correct or may be due to C_8-H and C_5-H protons respectively if structure Vd is correct. Since Set-A is almost identical with Set-C, structure Vc was assigned for the cyclization product. This corroborated the structure assigned earlier by Mohan and Pujari[2] and confirmed the validity of our method of calculation.

Table 1—Observed and Calculated Chemical Shifts in δ, ppm) for the Aromatic Protons (C_5-H and C_8-H) in Va, Vc and Vd

Structure	C_5-H		C_8-H	
	Calc.	Obs.	Calc.	Obs.
Va (DMSO-d_6)	—	7.33	—	7.15
Vc (DMSO-d_6)	7.42	7.47	7.58	7.57
Vd (DMSO-d_6)	7.76	7.57	7.24	7.47

The observed and calculated chemical shifts for aromatic protons (C_5-H and C_8-H) in Va, Vc and Vd are recorded in Table 1.

Biological activity

Antifungal activity—For fungicidal assay, the method of Aytoun *et al.*[4] was used. *Aspergillus flavus*, *Fusarium oxysporum* and *Sclerotium oryzae* were used as test fungi. Among the compounds (Va,b, VIIa,b and VIIIa,b) screened, only the thiazolidinones (Va and Vb) were found to be most active (100% inhibition at 1 : 500 dilution against all the fungi).

Antibacterial activity—Rideal-Walker[5] serial drop dilution method was used. The test organisms were 24 hr cultures of *Staphylococcus aureus* and *Escherichia coli*. The thiazolidinones (Va,b), thiazoles (VIIa,b) and dihydrothiazoles (VIIIa,b) were found to be more active (1 : 500 dilution) against *S. aureus* than *E. coli*.

Experimental Procedure

Melting points are uncorrected. TLC was performed on silica gel G plates using benzene-acetone (3 : 1) as irrigant. IR spectra were recorded in nujol mull on a Beckman IR-20 spectrophotometer (ν_{max} in cm^{-1}), PMR in DMSO-d_6 or TFA + $CDCl_3$ on a Perkin-Elmer 90 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm), and mass spectra on a Hitachi RMU-6D instrument at 70eV.

4,5-*Dinitroveratrol* (*IIa*)

To veratrol (Ia; 27.6g; 0.2mol) in acetic anhydride (100 ml), kept in ice-bath, conc. nitric acid (20 ml) was added dropwise with constant stirring. The reaction mixture was poured into ice cold water and the yellow solid, thus obtained was filtered and crystallized from ethanol to give IIa as yellow needles, m.p. 130° (lit.[6], m.p. 130-32°), yield 35 g (77%).

3,6-Dimethoxy-1,2-dinitrobenzene (IIb) was prepared in 70% yield by nitration of 1,4-dimethoxybenzene (Ib) in a similar manner, m.p. 175 (lit.[6], m.p. 177°).

5,6-*Dimethoxy*-2-*mercaptobenzimidazole* (*IIIa*)

It was prepared in 60% yield by the reduction of IIa with Raney nickel and hydrazine hydrate and subsequent reaction of the resulting diamine with carbon disulphide *in situ* following the method of Van Allan and Deacon[8] for the synthesis of 2-mercaptobenzimidazole, m.p. 275° (EtOH-DMF) (Found: S, 15.1. $C_9H_{10}N_2SO_2$ requires S, 15.2%); IR: 1630 (C = N), 2520-2680 (SH), 3040-3180 (NH).

4,7-Dimethoxy-2-mercaptobenzimidazole (IIIb) was similarly obtained from IIb, m.p. 238° (EtOH-DMF), yield 55% (Found: S, 15.1. $C_9H_{10}N_2SO_2$ requires S, 15.2%); IR: 1630 (C = N), 2580 (S – H), 3460 (NH).

5,6-*Dimethoxybenzimidazole*-2-*thiolacetic acid* (*IVa*)

A mixture of IIIa (2.1 g, 0.01 mol), chloroacetic acid (0.95 g, 0.01 mol) and KOH (1 g) in ethanol (20 ml) was heated under reflux for 3 hr, filtered out to remove insoluble impurities, and the filtrate diluted with water, acidified with dil. acetic acid and kept overnight. The solid, thus separated, was filtered, washed well with water and crystallized from ethanol to give IVa as white flakes, m.p. 235°, yield 2.0 g (72%) (Found: S, 11.8. $C_{11}H_{12}N_2SO_4$ requires S, 11.9%); IR: 1630 (C = N), 2360-2680 (CO_2H), 3040-3130 (NH).

4,7-Dimethoxybenzimidazole-2-thiolacetic acid (IVb) was obtained in a similar fashion from IIIb, as white flakes, m.p. 145°, yield 1.9 g, (71%) (Found: S, 11.9. $C_{11}H_{12}N_2SO_4$ requires S, 11.9%); IR: 1580 (C = C), 1640 (C = N), 2460-2740 (CO_2H), 3100-3200 (NH).

6,7-*Dimethoxythiazolo*[3,2-*a*]*benzimidazol*-3-(2*H*)-*one* (*Va*)

The acid IVa (1.0 g) in a mixture of acetic anhydride (1.0 ml) and pyridine (3.0 mg) was heated on a steam-bath for 15 min, cooled to room temperature and the solid, thus separated, was filtered, washed well with water and crystallized from ethanol to furnish Va as pale brown needles, m.p. 235°, yield 0.6 g (64%) (Found: S, 12.7. $C_{11}H_{10}N_2SO_3$ requires S, 12.8%); IR: 1600 (C = C), 1640 (C = N), 1730 (>N – CO –); PMR (DMSO-d_6): 3.77 (6H, *s*, 2 × OCH_3), 4.53 (2H, *s*, SCH_2), 7.15 (1H, *s*, C_8-H), 7.33 (1H, *s*, C_5-H); PMR (TFA + $CDCl_3$): 4.01 (3H, *s*, C_6-OCH_3 or C_7-OCH_3), 4.05 (C_7-OCH_3 or C_6-OCH_3), 4.72 (2H, *s*, SCH_2), 7.31 (1H, *s*, C_8-H), 7.68 (1H, *s*, C_5-H); MS: *m/z* 250 $[M]^{+\cdot}$.

Similarly, 5,8-dimethoxythiazolo [3,2-*a*]benzimidazol-3-(2*H*)-one (Vb) was obtained from IVb in 74% yield, as white needles, m.p. 177° (Found: S, 12.5. $C_{11}H_{10}N_2SO_3$ requires S, 12.8%); IR: 1610 (C = N), 1750 (>N – CO –), PMR (DMSO-d_6): 3.76

(3H, *s*, C_8-OCH_3), 3.82 (3H, *s*, C_5-OCH_3), 4.50 (2H, *s*, SCH_2), 6.76 (2H, broad *s*, Ar-H); PMR (TFA + $CDCl_3$): 3.99 (3H, *s*, C_8-OCH_3), 4.01 (3H, *s*, C_5-OCH_3), 4.75 (2H, *s*, SCH_2), 7.12 (2H, broad *s*, Ar-*H*); MS: *m/z* 250 $[M^{+}\cdot]$.

5,6-Dimethoxy-2-p-nitrophenacylthiobenzimidazole (VIa, R = p-$O_2NC_6H_4$)

A mixture of IIIa (2.1 g, 0.01 mol), *p*-nitrophenacyl bromide (2.44 g, 0.01 mol) in anhyd. EtOH-DMF (1 : 1; 50 ml) was heated under reflux for 3 hr, cooled to room temperature, poured into water, neutralized with sodium bicarbonate and kept overnight. The solid thus separated was filtered, washed well with water and crystallized from ethanol to give VIa (R = *p*-$O_2NC_6H_4$) as yellow needles, m.p. 240°, yield 2.5 g, (67%) (Found: S, 8.5. $C_{17}H_{15}N_3SO_5$ requires S, 8.6%); IR: 1600 (C = C), 1625 (C = N), 1685 (C = O), 3380-3580 (NH).

In a similar manner, VIb (R = *p*-BrC_6H_4) was obtained from the reaction of IIIb with *p*-bromophenacyl bromide as white flakes, m.p. 166° (EtOH), yield 2.7 g (66%) (Found: S, 7.8. $C_{17}H_{15}N_2SBrO_3$ requires S, 7.9%); IR: 1585 (C = C), 1670 (C = O), 3270 (NH).

6,7-Dimethoxy-3-p-nitrophenylthiazolo[3,2-a]benzimidazole (VIIa, R = p-$O_2NC_6H_4$)

VIa (R = *p*-$O_2NC_6H_4$, 1.0 g) in a mixture of phosphorus pentoxide (4 g) and orthophosphoric acid (3 ml) was heated on an oil-bath at 150° for 3 hr, cooled to room temperature, poured into iced-water and neutralized with sodium bicarbonate. The solid, thus obtained, was crystallized from ethanol to afford VIIa (R = *p*-$O_2NC_6H_4$) as white needles, m.p. 110°, yield 0.5 g (53%) (Found: S, 8.9. $C_{17}H_{13}N_3SO_4$ requires S, 9.0%); IR: 1595 (C = C); PMR (TFA + $CDCl_3$): 3.75 (3H, *s*, C_6-OCH_3 or C_7-OCH_3), 4.02 (3H, *s*, C_7-OCH_3 or C_6-OCH_3), 6.74 (1H, *s*, C_2-H), 7.30-8.68 (6H, *m*, Ar-*H*); MS: *m/z* 355 $[M]^{+}\cdot$.

Similarly, VIIb (R = *p*-BrC_6H_4) was obtained from VIb (R = *p*-BrC_6H_4) in 63% yield as white needles, m.p. 165° (EtOH) (Found: S, 8.2. $C_{17}H_{13}N_2SBrO_2$ requires S, 8.2%); IR: 1600 (C = C); PMR (TFA + $CDCl_3$): 3.36 (3H, *s*, C_5-OCH_3 or C_8-OCH_3), 4.00 (3H, *s*, C_8-OCH_3 or C_5-OCH_3), 6.79 (1H, *d*, C_6-H or C_7-H, $J_{6,7}$ = 9 Hz), 7.05 (1H, *d*, C_7-H or C_6-H, $J_{6,7}$ = 9 Hz), 7.19 (1H, *s*, C_2-H), 7.58 (4H, AB_q, *p*-BrC_6H_4); MS: *m/z* 388/390 (1 : 1) $[M^{+}\cdot]$.

6,7-Dimethoxy-3-methylthiazolo[3,2-a]benzimidazole (VIIa, R = CH_3)

A mixture of IIIa (2.1 g, 0.01 mol) and chloroacetone (0.93 g, 0.01 mol) in anhyd. EtOH-DMF (1 : 1; 50 ml) was heated under reflux for 3 hr, cooled to room temperature, poured into water, neutralized with sodium bicarbonate and kept overnight. The solid, thus separated, was filtered, washed well with water and crystallized from ethanol to furnish VIIa (R = CH_3) as white needles m.p. 180°, yield 1.8 g (72%) (Found: S, 12.7. $C_{12}H_{12}N_2SO_2$ requires S, 12.9%); IR: 1600 (C = C); PMR (TFA + $CDCl_3$): 2.92 (3H, broad *s*, CH_3), 4.01 (3H, *s*, C_6-OCH_3 or C_7-OCH_3), 4.05 (3H, *s*, C_7-OCH_3 or C_6-OCH_3), 6.99 (1H, broad *s*, C_2-H), 7.35 (1H, *s*, C_5-H or C_8-H), 7.52 (1H, *s*, C_8-H or C_5-H).

6,7-Dimethoxy-2,3-dihydrothiazolo[3,2-a]benzimidazole (VIIIa)

A mixture of IIIa (2.1 g, 0.01 mol) and 1,2-dibromoethane (1.88 g, 0.01 mol) in anhyd. EtOH-DMF (1 : 1 ratio, 50 ml) was heated under reflux for 3 hr, cooled to room temperature and poured into water. The hydrobromide thus obtained was neutralized with sodium carbonate to yield VIIIa as white needles, m.p. 155° (EtOH) yield 2.0 g (85%) (Found: S, 13.4. $C_{11}H_{12}N_2SO_2$ requires S, 13.6%); IR: 1590, 1630 (C = N, C = C); PMR (TFA + $CDCl_3$): 4.00 (3H, *s*, C_7-OCH_3 or C_6-OCH_3), 4.02 (3H, *s*, C_6-OCH_3 or C_7-OCH_3), 4.32 (2H, *t*, SCH_2), 4.73 (2H, *t*, NCH_2), 7.09 (1H, *s*, C_5-H, or C_8-H), 7.28 (1H, *s*, C_8-H or C_5-H); MS: *m/z* 236 $[M]^{+}\cdot$.

Similarly, VIIIb was prepared from IIIb and 1,2-dibromoethane, in 76% yield as white needles, m.p. 145° (EtOH) (Found: S, 13.5. $C_{11}H_{12}N_2SO_2$ requires S, 13.6%); IR: 1590, 1620 (C = C and C = N); PMR (TFA + $CDCl_3$): 3.96 (3H, *s*, C_5-OCH_3 or C_8-OCH_3), 3.97 (3H, *s*, C_8-OCH_3 or C_5-OCH_3), 4.29 (2H, *t*, SCH_2), 4.89 (2H, *t*, NCH_2), 6.90 (2H, broad *s*, Ar-*H*); MS: *m/z* 236 $[M]^{+}\cdot$.

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Condensed Heterocyclics: Part XX—Synthesis & Substitution Reactions of [1,2,5]Thiadiazolo- & [1,2,5]Selenadiazolo-[3,4-*f*]quinoline-N^6-oxides

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[1,2,5] Thiadiazolo- and [1,2,5] selenadiazolo-[3,4-*f*] quinoline-N^6-oxides (II) have been synthesised and their electrophilic and nucleophilic substitution reactions studied.

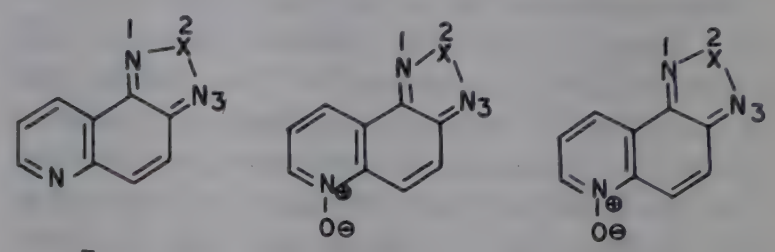
In view of the potential biological activity associated with the quinoline-N-oxide[1], 1,2,5-thiadiazole[2] and 1,2,5-selenadiazole[3] moieties and carcinogenic activity associated with pyridine-N-oxide[4], the title study was undertaken with the hope that the compounds synthesized being a combination of two biologically active systems might eventually exhibit important biological activities.

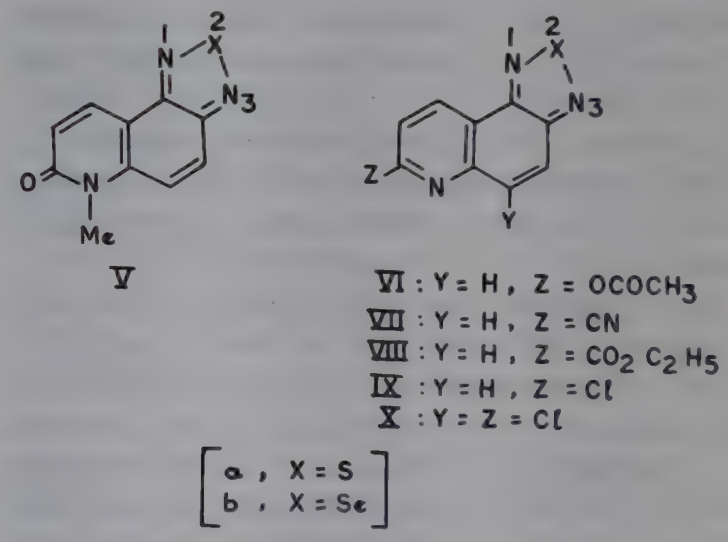
[1,2,5] Thiadiazolo [3,4-*f*] quinoline (Ia)[5] was oxidised to [1,2,5] thiadiazolo [3,4-*f*] quinoline-N^6-oxide (IIa) with *m*-chloroperbenzoic acid. A similar oxidation of [1,2,5] selenadiazolo [3,4-*f*] quinoline (Ib) gave [1,2,5] selenadiazolo [3,4-*f*] quinoline-N^6-oxide (IIb). Both the products (IIa, b) were characterized by their slow mobility on TLC and by IR and PMR data.

The N^6-oxide IIa on treatment with benzoyl nitrate afforded 8-nitro [1,2,5] thiadiazolo [3,4-*f*] quinoline-N^6-oxide (IIIa). The entry of nitro group in the ring was confirmed by IR spectrum, analogy[6] as well as by PMR spectrum of IIIa in DMSO-d_6 which exhibited two *AB* quartets assignable to H-4/H-5 ($J_{4,5}=9$Hz) and H-7/H-9 ($J_{7,9}=1.8$Hz) protons. Since the quartet due to H-3, typical of the pyridine ring was missing and the *AB* quartet due to H-4/H-5 was observed, it was concluded that nitro group had entered the pyridine ring and thus structure III was assigned to the product. The selenium analogue (IIb) on treatment with benzoyl nitrate in a similar fashion gave 8-nitro-[1,2,5] selenadiazolo [3,4-*f*] quinoline-N^6-oxide (IIIb).

The compound IIa on treatment with a mixture of fuming nitric acid and sulphuric acid afforded a product which was characterised as 9-nitro-[1,2,5] thiadiazolo [3,4-*f*] quinoline-N^6-oxide (IVa) on the basis of its IR and PMR spectra. However, a similar treatment of IIb resulted in ring fission giving the selenium metal in about 80% yield.

The reaction of IIa with benzoyl chloride in





methylene chloride and sodium hydroxide under Reissert's condition[7,8] provided a compound whose IR spectrum displayed an absorption band at 1680 cm^{-1} suggesting it to be a carbostyryl derivative 6,7-dihydro [1,2,5] thiadiazolo [3,4-*f*] quinolin-7-one (Va). Its structure was further corroborated by its PMR spectrum. IIb when reacted with benzoyl chloride under identical conditions gave 6,7-dihydro-[1,2,5] selenadiazolo [3,4-*f*] quinolin-7-one (Vb).

The N^6-oxide IIa when heated under reflux with acetic anhydride provided 7-acetoxy-[1,2,5] thiadiazolo [3,4-*f*] quinoline (VIa) whose structure was based on the appearance of a carbonyl absorption

band at 1660 cm^{-1} in its IR spectrum and three-proton singlet due to acetoxy methyl at δ 1.10 in the PMR spectrum. The extraordinary upfield shift of this methyl signal was corroborated by a comparison with the PMR spectrum of 2-acetoxyquinoline, prepared by reacting quinoline-N-oxide with acetic anhydride, in which the methyl protons resonated at δ 1.15 in $CDCl_3$ solution. This may be due to anisotropy of the ring current as the methyl group falls in the shielding region having deviated from the plane of the ring due to dipole-dipole repulsion of the lone pair of electrons on nitrogen and the carbonyl group. A similar reaction of IIb with acetic anhydride gave 2-acetoxy-[1,2,5] selenadiazolo [3,4,-*f*] quinoline (VIb) whose PMR spectrum displayed a three-proton singlet at δ 1.12 in support of the assigned structure VIb.

The compound IIa on treatment with aq. KCN under Reissert's condition[9] afforded 7-cyano-[1,2,5] thiadiazolo [3,4-*f*] quinoline (VIIa) in a good yield (59.5%) whose IR spectrum exhibited νCN band at 2230 cm^{-1}. The structure assignment of VIIa was based on analogy alone as it was sparingly soluble in most of the organic solvents and thus its PMR spectrum could not be recorded. The compound VIIa was refluxed with abs. ethanol containing a catalytic amount of conc. sulphuric acid and the product on purification by preparative TLC provided 7-carbathoxy-[1,2,5] thiadiazolo [3,4-*f*] quinoline (VIIIa) in 48.0% yield. Its formation was corroborated by the appearance of a νCO at 1680 cm^{-1} and the disappearance of νCN band from its IR spectrum.

The N^6-oxide IIb on reaction with KCN in a similar manner as described above gave 7-cyano-[1,2,5] selenadiazolo [3,4-*f*] quinoline (VIIb) in 47% yield.

The compound was heated under reflux with phosphorus oxychloride with the hope of getting 7-chloro-[1,2,5] thiadiazolo [3,4-*f*] quinoline (IXa), but surprisingly the experiment ended with the formation of 5,7-dichloro-[1,2,5] thiadiazolo [3,4-*f*] quinoline (Xa) as evidenced by its elemental analysis and PMR spectrum. However, when IIb was reacted with phosphorus oxychloride under reflux, it provided the expected 7-chloro-[1,2,5] selenadiazolo [3,4-*f*] quinoline in 47% yield.

Experimental Procedure

Melting points are uncorrected. PMR spectra were recorded on a Perkin-Elmer R-32 90 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and IR spectra on Backman IR-120 and SP-1200 spectrophotometers (ν_{max} in cm^{-1}).

[1,2,5] *Thiadiazolo* [3,4-*f*] *quinoline-N^6-oxide* (*IIa*)

A solution of [1,2,5] thiadiazolo [3,4-*f*] quinoline (Ia; 1.87 g, 0.01 mol) in dry methylene chloride was cooled to 0° and *m*-chloroperbenzoic acid (3.5 g, 0.02 mol) in dry methylene chloride (12 ml) added to it dropwise (*ca.* 1.5 hr) with vigorous stirring maintaining the temperature of the reaction mixture below 0°. After the addition was over, the reaction mixture was further stirred for 30 min, then refluxed on a water-bath for 30 min, dry ammonia passed until saturation and the resultant precipitate filtered. Removal of solvent from the filtrate followed by column chromatography afforded TLC-pure IIa as light yellow crystals, yield 1.4 g (70%), m.p. 225-26° (Found: C, 53.1; H, 2.8; N, 20.3; S, 15.7. $C_9H_5N_3SO$ requires C, 53.2; H, 2.5; N, 20.7; S, 15.8%), IR (nujol): 1275 (N→O); PMR ($CDCl_3$); 8.85 (1H, *dd*, H-5), 8.65 (1H, broad *d*, H-7), 8.55 (1H, *d*, H-9), 8.10 (1H, *dd*, H-4), 7.56 (1H, *q*, H-8), ($J_{4,5}=9$, $J_{7,8}=4.0$, $J_{7,9}=2.0$Hz).

[1,2,5] *Selenadiazolo* [3,4-*f*] *quinoline-N^6-oxide* (*IIb*)

[1,2,5] Selenadiazolo [3,4-*f*] quinoline (Ib; 2.33 g, 0.01 mol) was reacted with *m*-chloroperbenzoic acid (3.5 g; 0.02 mol) in dry methylene chloride (15 ml) following the procedure described above to give IIb, yield 1.8 g (72%), m.p. 264-65° (Found: C, 43.1; H, 2.0; N, 16.9. $C_9H_5N_3SeO$ requires C, 43.4; H, 2.0; N, 16.9%); IR (KBr): 1260 cm^{-1} (N→O); PMR ($CDCl_3$): 9.27 (1H, *dd*, H-9), 9.05 (1H, *d*, H-7), 8.60 (1H, *d*, H-5), 8.20 (1H, *dd*, H-4), 7.92 (1H, pseudo *q*, H-8), ($J_{4,5}=10$, $J_{7,8}=5$, $J_{7,9}=2.0$, $J_{8,9}=8$Hz).

8-*Nitro*-[1,2,5] *thiadiazolo* [3,4-*f*] *quinoline-N^6-oxide* (*IIIa*)

Benzoyl chloride (0.56 g, 0.004 mol) in dichloromethane (10 ml) was gradually added to the stirred solution of silver nitrate (1.(0 g; 0.006 mol) in dry dichloromethane (10 ml) and the mixture vigorously stirred for 15 min. The solution was quickly filtered and the filtrate transferred to a separatory funnel and gradually added to an ice-cold solution of IIa (0.40 g, 0.002 mol) in dry dichloromethane at such a rate so as to maintain the temperature below 0°, and the stirring continued for 30 min. The reaction mixture was further stirred at room temperature for 2 hr then refluxed on a water-bath for 30 min, cooled, dry ammonia passed until saturation and the precipitate filtered. Removal of solvent from the filtrate gave a residue which was passed through a column of silica gel and eluted with benzene. The eluate was stripped off of the solvent to give IIIa as a yellow solid, yield 0.25 g (54.3%), m.p. 230° (Found: C, 43.2; H, 1.4; N, 22.1; S, 12.7. $C_9H_4N_4O_3S$ requires C, 43.5; H, 1.6; N, 22.6; S, 12.9%); IR (KBr): 1520, 1340 (NO_2), 1220 (N→O); PMR (DMSO): 9.55 (1H, *d*, H-7); 8.45 (1H, *d*, H-9), 8.30 (2H, *q*, H-4 and H-5) ($J_{7,9}=1.8$, $J_{4,5}=9$Hz).

8-*Nitro*-[1,2,5] *Selenadiazolo* [3,4-*f*] *quinoline-N^6-oxide* (*IIIb*)

The selenium analogue IIb (0.99 g, 0.004 mol) was reacted with benzoyl nitrate, obtained from benzoyl chloride (1.12 g, 0.08 mol) in dry dichloromethane (20 ml) and silver nitrate (2.0 g, 0.012 mol) according to the procedure described for IIIa, to obtain IIIb as TLC-pure yellow compound, yield 0.5 g, m.p. 217-18° (Found: C, 36.5; H, 1.4; N, 19.2. $C_9H_4N_4O_3Se$ requires C, 36.7; H, 1.4; N, 19.0%); IR (KBr): 1530, 1350 (NO_2), 1225 (N→O).

9-*Nitro*-[1,2,5] *thiadiazolo* [3,4-*f*] *quinoline-N^6-oxide* (*IVa*)

Compound IIa (0.4 g, 0.002 mol) was dissolved in a minimum quantity of conc. sulphuric acid (*ca.* 10 ml) at 0° and to this well stirred and cooled solution was added fuming nitric acid (*ca.* 3 ml) in small portions so as to maintain the temperature at 0°. The stirring was continued for another 2 hr at room temperature and finally the reaction mixture refluxed on a water-bath for 1 hr, cooled, poured into ice water (100 ml), basified with ammonia and the organic material taken up in chloroform. Usual work-up including column chromatography provided 0.22 g (44.8%) of IVa as a light yellow compound, m.p. 226-27° (Found: C, 43.3; H, 1.6; N, 22.5; S, 12.9%); IR (KBr): 1560, 1350 (NO_2), 1220 (N→O); PMR ($CDCl_3$): 8.92 (1H, *d*, H-7), 8.72 (1H, *d*, H-5), 8.33 (1H, *d*, H-4), 8.30 (1H, *d*, H-8), ($J_{7,8}$ = 4.5, $J_{4,5}$ = 9Hz).

Tautomeric 6,7-*dihydro*-[1,2,5] *thiadiazolo* – [3,4-*f*] *quinolin-7-one* (*Va*)

To a solution of IIa (0.40 g, 0.002 mol) in methylene chloride (10 ml) was gradually added benzoyl chloride (0.7 g, 0.006 mol) in methylene chloride and then sodium hydroxide (0.22 g, 0.004 mol) in water (5 ml) with cooling and stirring (*ca.* 1.5 hr). After the completion of addition, stirring was continued at room temperature for 2 hr, water (100 ml) added and the methylene chloride layer separated. The aq. layer was extracted with methylene chloride (2 × 50 ml). The combined methylene chloride layer was washed with water, dried (Na_2SO_4), solvent removed and the residue chromatographed using pet. ether-benzene (20:80) as eluent to afford the desired compound, yield, 0.25 g (62.5%), m.p. 196-97° (Found: C, 52.8; H, 2.3; N, 20.7; S, 15.7. $C_9H_5N_3SO$ requires C, 53.2; H, 2.5; N, 20.7; S, 15.8%; IR (KBr): 1740 (C=O), 3200-3400 (br, OH); PMR ($CDCl_3$): 9.18 (1H, *d*, H-9), 8.35 (1H, *dd*, H-8), 8.12 (1H, *d*, NH), 7.64 (1H, *dd*, H-4), 7.53 (1H, *d*, H-5) ($J_{8,9}$ = 8.5, $J_{6,8}$ = 2.0, $J_{4,6}$ = 0.5Hz).

6,7-*Dihydro*-7-*oxo*-[1,2,5] *selenadiazolo* – [3,4-*f*] *quinoline* (*Vb*)

Compound IIb (0.62 g, 0.0025 mol) was reacted with benzoyl chloride (1.05 g, 0.0075 mol) in dry methylene chloride and sodium hydroxide (0.20 g, 0.005 mol) in water (5 ml), following the procedure as described for Va, to give Vb, yield 0.20 g (32.3%), m.p. >300° (Found: C, 43.2; H, 1.8; N, 16.9. $C_9H_5N_3SeO$ requires C, 43.4; H, 2.0; N, 16.9%); IR (KBr): 1740 (C=O), 3200-3400 (br, OH), PMR ($CDCl_3$ + TFA): 8.95 (1H, *d*, H-9), 8.20 (1H, *dd*, H-4), 8.05 (1H, *d*, NH), 7.75 (1H, *d*, H-5), 7.45 (1H, *d*, H-8) ($J_{4,5}$ = 10, $J_{8,9}$ = 9, $J_{6,8}$ = 2, $J_{4,6}$ = 0.5Hz).

7-*Acetoxy*-[1,2,5] *thiadiazolo* [3,4-*f*] *quinoline* (*VIa*)

Acetic anhydride (5 ml) in dry methylene chloride (5 ml) was added to a vigorously stirred solution of IIa (0.4 g, 0.002 mol) in dry methylene chloride (10 ml) at room temperature for about 30 min. Thereafter, the reaction mixture was refluxed on a water-bath for 8 hr, cooled, poured in ice-cold water, basified with liquor ammonia and methylene chloride layer separated. The aq. layer was extracted with methylene chloride (2 × 100 ml). The combined extract was washed with water, dried (Na_2SO_4) and solvent removed. The residue on column chromatography followed by sublimation *in vacuo* afforded VIa, yield 0.2 g (40.8%), m.p. >300° (Found: C, 53.6; H, 2.7; N, 17.3; S, 12.9. $C_{11}H_7N_3SO_2$ requires C, 53.9; H, 2.9; N, 17.1; S, 13.1%); IR (nujol): 1660 (C=O); PMR (TFA): 9.85 (1H, *d*, H-9), 8.62 (1H, *d*, H-5), 8.50 (1H, *d*, H-4), 8.43 (1H, *d*, H-8), 1.35 (3H, *s*, C-Me) ($J_{4,5}$ = 9, $J_{8,9}$ = 8.5Hz).

7-*Acetoxy*-[1,2,5] *selenadiazolo* [3,4-*f*] *quinoline* (*VIb*)

The N^6-oxide IIb (0.373 g, 0.0015 mol) was heated under reflux in acetic anhydride (5 ml) and methylene chloride (5 ml) for 8 hr, under the conditions as described for VIa to obtain the desired product (VIb), yield 0.16 g (36.6%), m.p. 175-76° (Found: C, 45.5; H, 2.42; N, 14.6. $C_{11}H_7N_3SeO_2$ requires C, 45.4; H, 2.4; N, 14.4%); IR (KBr): 1680 (C=O); NMR ($CDCl_3$ + TFA): 9.10 (1H, *d*, H-9), 8.20 (2H, degenerate *q*, H-4 and H-5), 8.0 (1H, br *d*, H-8), 1.10 (3H, *s*, CH_3) ($J_{4,5}$ = $J_{8,9}$ = 8.5Hz).

7-*Cyano*-[1,2,5] *thiadiazolo* [3,4-*f*] *quinoline* (*VIIa*)

A solution of KCN (0.3 g, 0.006 mol) in water (5 ml) was added to IIa (0.4 g, 0.002 mol) in methylene chloride (10 ml). Thereafter, benzoyl chloride (0.42 g, 0.006 mol) in methylene chloride (10 ml) was added gradually to the above vigorously stirred reaction mixture and stirring continued further for 6 hr. The

organic layer was separated, washed well with water, dried ($MgSO_4$), solvent removed and the residue chromatographed over silica gel column using benzene as eluent to afford VIIa as a white crystalline solid, yield 0.25 g (60%), m.p. 260-61° (Found: C, 56.4; H, 1.6; N, 26.2; S, 15.2. $C_{10}H_4N_4S$ requires C, 56.6, H, 1.9; N, 26.4; S, 15.0%); IR (KBr): 2230 (C≡N); PMR ($CDCl_3$ + TFA): 9.30 (1H, *d*, H-9), 8.31 (1H, *d*, H-8), 8.15 (2H, degenerate *q*, H-4 and H-9) ($J_{4,5} = J_{8,9} = 9$Hz).

7-Cyano-[1,2,5] *selenadiazolo* [3,4-*f*] *quinoline* (*VIIb*)

Compound IIb (0.62 g, 0.0025 mol) in methylene chloride (10 ml) was treated with benzoyl chloride (1.05 g; 0.0072 mol) in methylene chloride (10 ml) following the method as used for VIIa. Usual work-up of the reaction mixture provided VIIb as a white solid, yield 0.30 g (47%), m.p. 260-61° (Found: C, 46.6; H, 1.7; N, 21.4. $C_{10}H_4N_4Se$ requires C, 46.5; H, 1.6; N, 21.7%); IR (KBr): 2210 (C≡N); PMR ($CDCl_3$ + TFA): 9.33 (1H, *d*, H-9), 8.34 (1H, *d*, H-8), 8.20 (2H, degenrate *q*, H-4 and H-5) ($J_{4,5} = 9$Hz).

7-Carbethoxy-[1,2,5] *thiadiazolo* [3,4-*f*] *quinoline* (*VIIIa*)

To the cyano compound VIIa (0.21 g, 0.001 mol) taken in conc. sulphuric acid (8 ml) was added abs. ethanol (10 ml) and the reaction mixture refluxed on a water-bath for 6 hr, poured onto crushed ice and the organic material taken up in chloroform. The aq. layer was extracted with chloroform (2 × 100 ml). The combined extract was dried ($MgSO_4$) and worked-up as usual to provide VIIIa as white crystals, yield 0.12 g (48%), m.p. 209-10° (Found: C, 55.5; H, 3.6; N, 15.8; S, 12.4. $C_{12}H_9N_3SO_2$ requires C, 55.6; H, 3.5; N, 16.2; S, 12.4%); IR (KBr): 1760 (C=O).

5,7-Dichloro-[1,2,5] *thiadiazolo* [3,4-*f*] *quinoline* (*IXa*)

The N^6-oxide IIa (0.40 g; 0.002 mol) was refluxed with excess of phosphorus oxychloride (3 ml) for 3 hr. After cooling, the reaction mixture was poured into cold water and basified with ammonia (1:1). The organic material was taken up in chloroform and the aqueous layer extracted twice with chloroform (2 × 100 ml). The combined chloroform extract was washed with water, dried ($MgSO_4$) and the solvent stripped off. The residue on purification by passing through a column of silica gel using pet. ether-benzene (50:50) as eluent gave IXa as a white compound, yield 0.19 g (37.2%), m.p. 196-97° (Found: C, 41.8; H, 1.2; N, 16.1; S, 12.3. $C_9H_3N_3SCl_2$ requires C, 42.2; H, 1.2; N, 16.4; S, 12.50%); PMR ($CDCl_3$): 9.05 (1H, *s*, H-4); 8.95 (1H, *d*, H-9); 7.72 (1H, *d*, H-8) ($J_{8,9} = 8.5$Hz).

7-Chloro-[1,2,5] *selenadiazolo* [3,4-*f*] *quinoline* (*IXb*)

The N^6-oxide IIa (0.498 g; 0.002 mol) was refluxed with excess of phosphorous oxychloride (8 ml) for 3 hr. After cooling, the reaction mixture was poured into cold water and basified with ammonia (1:1). The organic material was taken up in chloroform and the aq. layer extracted with chloroform (2 × 100 ml). The combined chloroform extract was washed with water, dried (Na_2SO_4) and the solvent stripped off. The residue was purified by passing through a column of silica gel using pet. ether-benzene (60:40) as eluent which afforded the desired compound (IXb) as a light yellow solid, yield 0.25 g (47%), m.p. 249-50° (Found: C, 40.2; H, 1.4; N, 15.9. $C_9H_4N_3SeCl$ requires C, 40.4; H, 1.5; N, 15.7%); PMR ($CDCl_3$ + TFA): 9.05 (1H, *d*, H-9), 8.00 (2H, degenerate *q*, H-4 and H-5), 7.70 (1H, *d*, H-8) ($J_{8,9} = 9$Hz).

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Formation of Mesoionic Thiazolo[3,2-*a*]pyrimidines from 2-Thiouracil Derivatives

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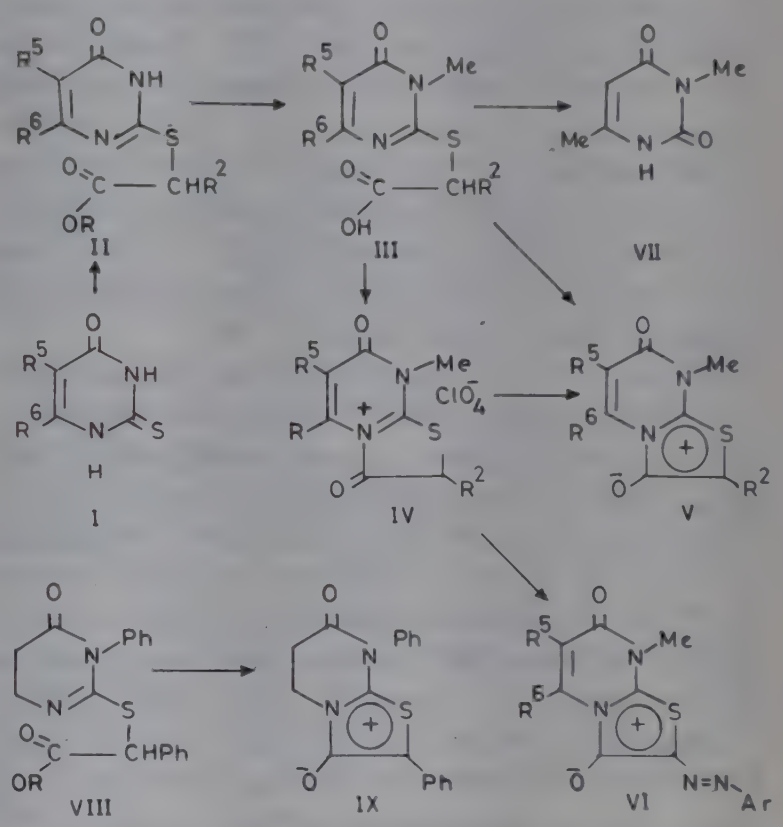
Carboxymethylthio derivatives (III, R^2 = H,Ph) from some 2-thiouracil derivatives(I) show considerable variation in their solubility behaviour in water and stability towards various reagents. Cyclodehydration of III(R^2 = Ph) and VIII (R = H) proceeds normally to give yellow mesoionic systems (V,R^2 = Ph; IX) but thiazolium perchlorate salt (IV) of III(R^2 = H) is a more useful intermediate for generation of mesoionic compounds (V VI). The assigned structures are supported by elemental analyses, UV IR and mass spectra.

Thiouracil derivatives (I) are reported[1-3] to possess a variety of biological activities and the occurrence of thiazole ring in biologically important compounds is also well known. In this context, we report herein the syntheses and properties of some mesoionic thiazolo[3,2-*a*]pyrimidinium derivatives derived from I.

In contrast to our previous observation[4] we have noted that the reactivity of I is governed by the nature of substituents at C-5 and C-6. For instance, isolation of S-carboxymethyl derivative from Ib via sodium chloroacetate condensation was difficult on account of its high water solubility, whereas formation of IIa,c,e (R = H) was facile, as expected[4]. Similarly, condensation of ethyl α-chlorophenyl acetate with Ia,b was extremely sluggish but condensation with Ic,d as well as with 3-phenyl-5,6-dihydro-2-thiouracil[5] furnished the respective products (II,R = Et and VIII) in modest yields. The structures of IIb,d,f (R = Et) were supported by the presence of additional ν C=O around 1740 cm^{-1}; in addition IIf (R = Et) exhibited ν N−H at 3485 and 3310 cm^{-1}. Moreover, UV absorption bands around 240 and 270 nm in alkaline medium provided additional support to the structures (see ref. 2). In contrast, VIII (R = Et) exhibited only one band at 220 nm, and this is presumably due to lack of conjugation[2] at 5,6-positions of the uracil ring in VIII. Finally, esters like II or VIII (R = Et) might as well exist in their lactam form[4a] but we have not considered this aspect since it is not going to affect the conclusions.

As expected[6,7], the acids (II, R = R^2 = H) or the α-phenyl esters (II, R = Et, R^2 = Ph), which are readily hydrolysed by aqueous alkali under mild condition, on treatment with dimethyl sulphate and aqueous alkali directly furnished the corresponding N^3-methyl substituted acids (IIIa,c,d,f). Conformations of structures of III was provided by their UV spectra, and acid hydrolysis (6*N* HCl, 6 hr) of representative



Compd		R^2	R^5	R^6
I, VI	a	-	H	H
	b	-	Me	H
	c	-	H	Me
	d	-	H	NH_2
II-V	a	H	H	H
	b	Ph	H	H
	c	H	H	Me
	d	Ph	H	Me
	e	H	H	NH_2
	f	Ph	H	NH_2
	g	ArCO	H	Me

compounds like IIIc and IIId which furnished the reported[7] 3,6-dimethyluracil (VII). However, except for IIIa,c,d,f, sufficient quantity of the acid IIIe could not be isolated on account of its high water solubility, for subsequent studies on cyclodehyddration of acids III.

Isolation of mesoionic compounds via cyclodehydration of IIIa proved to be more difficult than structurally related acids based on 4-quinazolone system[4] and no TLC pure compounds could be isolated. Nonetheless, Δ^2-thiazolium perchlorate salts (IVa,c) were readily obtained from IIIa,c with acetic anhydride and 70% perchloric acid. Subsequent diazo coupling[8] of IVa,c readily furnished the expected deep red azo-derivatives (VI) whereas IIIa,c did not respond to this reaction. Similarly, aroylation of IVc in the presence of triethylamine gave yellow mesoionic ketones (Vg; M^+, 345 when Ar = *p*-NO_2.Ph) but acylation of IVa with acetic anhydride and pyridine was unsuccessful. Finally, deprotonation of IVc also yielded the mesoionic system Vc whereas IVa failed to give analytically pure Va although the spectral data of Va compared favourably with Vc. Again IIId on cyclodehydration smoothly furnished the desired mesoionic compound Vd (M^+, 272) identical (IR, TLC, m.m.p.) with that generated from the corresponding Δ^2-thiazolium salt (IVd). Similar cyclodehydration of IIIf furnished Vf (M^+, 273), and VIII yielded a relatively unstable and difficult to purify compound (IX). But spectral data of a fairly pure (TLC) sample of IX were similar to those of other well-defined mesoionic compounds (V, VI).

Evidence in favour of mesoionic structures are based on elemental analyses, IR, UV absorption characteristics[4,8] (e.g. loss of colour on protonation and blue shift in λ_{max} with increasing polarity of the solvent) and mass fragmentation pattern of representative compounds, like Vd, Vf, Vg (Ar = *p*-NO_2.Ph) and VIa (Ar = *p*-MePh). An interesting feature of the mass spectra is the presence of intense M^+ peaks in cases other than the azo-derivative[8]. It appears that the primary fragmentation occurs via thiazole ring, as noted earlier[8], with the generation of fragments at *m/z* 142, 156, 157 (2-thiopyrimidine-4-one unit), 150 (*p*-NO_2.Ph.CO^+), 121 (Ph.CS^+) and 119 (*p*-Me-Ph.N_2^+) in agreement with assigned structures. Another common strong peak at *m/z* 83 indicates facile cleavage of 4-pyrimidone ring (with loss of R-$\overset{6}{C}$ = $\overset{5}{C}$-H moiety) under electron impact.

Experimental Procedure

Melting points were determined in open capillaries and are uncorrected. Unless otherwise stated UV spectra were recorded in methanol on a Hitachi-200-20 spectrophotometer (λ_{max} in nm and ε values in parentheses) and IR spectra in KBr on a Perkin-Elmer 157G spectrophotometer; only the significant bands (ν_{max} in cm^{-1}) are quoted. TLC plates coated (0.25 mm) with silica gel G developed with benzene-acetonitrile (1:1, v/v) at room temperature (~ 27°).

S-Carboxymethyl-2-thiouracil derivatives (II). (A) via sodium chloroacetate condensation with I

To a solution of required I (1 g) in aq NaOH (2 equiv in 10 ml water) was added a solution of sodium chloroacetate (3 equiv) in water (5 ml) in one lot, stirred for 3 hr at room temperature, and acidified with 6*N* HCl to afford a white crystalline material (II) purified via $NaHCO_3$ treatment and crystallisation.

IIa (R = H): off-white shining needles (acetone), m.p. 177-78°(d); yield, 90%; UV: 228(5,910), 287(5,940); + 0.1*N*. NaOH: 243(5,813), 276(4,940); (Found: S, 17.4. $C_6H_6N_2O_3S$ requires S, 17.2%).

IIc (R = H): white shinging shining needles (acetone), m.p.203-4°(d); yield 80%; UV: 232(8,200) and 284(6,720); + 0.1*N* NaOH: 245(6,736), 275(5,000); IR: 3000-2400(br), 1725, 1660(C=O), 1630(C=N) (Found: S, 16.1. $C_7H_8N_2O_3S$ requires S, 16.0%).

IIe (R = H): white shining needles (EtOH), m.p. 227-28°(d); yield 70%; UV: 230sh, (13,860), 273(6,588); + 0.1*N* NaOH: 221(20,300), 263(10,820); IR: 3480, 3370(N−H), 2800-2740(br), 1710, 1610 (Found: S, 15.8. $C_6H_7N_3O_3S$ requires S, 15.9%).

(B) via condensation with α-chlorophenyl acetate

A mixture of I (1 g), α-chloroacetate ester (1.2 equiv), anhydrous potassium carbonate (1 g) and DMF (0.5 ml) in dry acetone (50 ml) was refluxed for 12-18 hr on a steam-bath, cooled, filtered and the filtrate concentrated. The gummy residue on boiling with pet.ether and cooling afforded the desired esters which were purified by crystallisation. In the case of VIII the semi-solid residue obtained after removal of acetone was again boiled with benzene and filtered. The solid residue was found to be unreacted I (*ca* 50%). Removal of benzene left an oily residue which was again treated with hot pet.ether to get VIII as a solid.

IIb (R = Et): white granules (acetone), m.p. 152-53°; yield ~ 5%; UV: 220 (12,480), 283(6,186); IR: 1735, 1660(C=O) (Found: C, 57.7; H, 4.7; S, 11.0. $C_{14}H_{14}N_2O_3S$ requires C, 57.9; H, 4.8; S, 11.0%).

IId (R = Et): white shining needles (dichloromethane-pet.ether), m.p. 115°; R_f 0.50; yield, 80%; UV: 220(17,000), 280(7,990); IR: 1745, 1655(C=O) (Found: C, 59.0; H, 5.1; S, 10.5. $C_{15}H_{16}N_2O_3S$ requires C, 59.2; H, 5.3; S, 10.5%).

Alkaline hydrolysis of the above ester (304 mg and 0.5 ml of 20% NaOH) at room temperature for 3 hr and subsequent acidification with 6*N* HCl readily gave the corresponding acid (IIId, R = H) as off-white cubes (210 mg, 77%), m.p. 199-200°(d), (aq MeOH); UV: 223(12,600), 287(8,490); IR: 3000-2700(br), 1705, 1665(C=O) (Found: S, 11.3. $C_{13}H_{12}N_2O_3S$ requires S, 11.6%).

IIf (R = Et): white shining granules (acetone-pet.ether), m.p. 178-79°; R_f 0.14; yield 33%; UV: 220(15,870), 270(6,225), IR: 3485, 3310 (N – H); 1735, 1609 (Found: C, 54.9; H, 4.8; S, 10.5. $C_{14}H_{15}N_3O_3S$ requires C, 55.1; H, 4.9; S, 10.5%).

VIII (R = Et): pale yellow shining needles (EtOH), m.p. 131-32°; R_f 0.71; yield 45% (based on thione consumed); UV: 220(19,400) (Found: C, 65.1; H, 5.5; S, 8.7. $C_{20}H_{20}N_2O_3S$ requires C, 65.2; H, 5.4; S, 8.7%).

3-Methyl-S-carboxymethyl-2-thiouracil derivatives (III)

Me_2SO_4 (1.2 equiv) was added dropwise to a solution of II(R = H or Et; 10 mmol) in aq NaOH (3 equiv in 7.5 ml of water) under agitation, maintaining the *p*H around 9 by occasional addition of alkali. The mixture was acidified with gl HOAc after 2 hr, cooled in an ice-bath and saturated with sodium chloride when white solid slowly separated from the mixture. It was collected, washed with ice-water and purified via $NaHCO_3$ treatment.

IIIa: white crystals, m.p. 192-93°(d); yield 55%; UV: 232(7,925), 292(5,280) + 0.1*N* NaOH: 234(8,290), 291(5,640); IR: 2800-2400(br), 1725, 1620 (Found: S, 15.9. $C_7H_8N_2O_3S$ requires S, 16.0%).

IIIc: colourless needles (acetone), m.p. 194-95°(d); yield 71%; UV: 223(5680), 237sh, 288(9,000); + 0.1*N* NaOH : 239(3,550), 287(7,620); IR: 3000-2400(br); 1720, 1635 (C = O) (Found: S, 15.0. $C_8H_{10}N_2O_3S$ requires S, 15.0%).

IIId: semi-solid gum at room temperature and decomposed on attempted crystallisation. It was extracted with dry chloroform-ether mixture and directly used in the next step, viz preparation of IVd.

IIIf: white solid, unstable at room temperature, it was quickly taken up in methanol-benzene, evaporated and the syrupy residue immediately used for cyclodehydration (see below, V).

VIII(R = H): also obtained as semi-solid gum, could not be crystallised and it was directly cyclised as in IIIf.

Δ^2-Thiazolium perchlorate salts (IV)

To an ice cold suspension of III (200 mg) in acetic anhydride (3 ml), $HClO_4$ (0.3 ml, 70%) was added dropwise under agitation when a clear solution was obtained. The reaction mixture was stirred for 2 hr at room temperature, diluted with enough dry ether, separated salts were collected, washed thoroughly with dry ether, dried in the air and crystallised from acetone.

IVa: white granules, m.p. 182-84°(d); yield 78% (Found: S, 11.3. $C_7H_7ClN_2O_6S$ requires S, 11.3%).

IVc: white shining granules, m.p. 201-2 (d); yield 60%; IR: 1795 and 1720(C = O), 1645(C = N) (Found: S, 11.0. $C_8H_9ClN_2O_6S$ requires S, 10.8%).

IVd: The gummy salt could not be crystallised and was directly used for deprotonation (see below).

Anhydro-1-hydroxy-4(H)-methyl-5-oxothiazolo[3,2-a]pyrimidinium hydroxide (V) (A): 1): Depro-Deprotonation of perchlorate salts (IV)

The salt (IV, 300 mg) was suspended in dry benzene (10 ml) and to this was added a mixture of pyridine (2.5 ml) and triethylamine (1 ml) dropwise with stirring at room temperature. The yellow mesoionic compound (V) was collected after 1 hr, washed with benzene, water, acetone, dried in the air and finally crystallised or repeatedly washed with warm solvent for spraingly soluble material.

Va: moderately pure (TLC) yellow material, m.p. 210-12°(d); IR: 1720, 1625. It is fairly soluble in water and it was subsequently characterised via azo-derivative (VI).

Vc: pale yellow flakes, m.p. 206-7°(d); sparingly soluble in common organic solvents; R_f 0.32; yield 50.32%; UV (qualitative, MeCN): 240, 272, 355 (355 band shifted to 365 nm in benzene); IR: 1715 (C = O, polar), 1665 (C = O, amide) (Found: C, 48.8; H, 4.0; S, 16.3. $C_8H_8N_2O_2S$ requires C, 49.0; H, 4.1; S, 16.3%).

Vd: deep yellow needles (MeCN), m.p. 200-201°(d), R_f 0.48; yield 80%; UV (MeCN): 226(12,400), 283(14,000), 370(8,900), 440sh (~ 3,880) (440 nm band shifted to 465 nm in benzene); yellow colour in MeCN also disappears on protonation; IR: 1710 (C = O, polar), 1675 (C = O, amide); MS: *m/z* (rel. intensity): 272(100, M^+), 156(80, 3,6-dimethyl-2-tihiopyrimidine-4-one), 123(100, 156 – SH), 121(60, $Ph.CS^+$), 83(70, 123 – Me.C ≡ CH), 68(20, 83 – Me) (Found: C, 61.5; H, 4.4;S, 11.7. $C_{14}H_{12}N_2O_2S$ requires C, 61.8, H, 4.4; S, 11.8%).

(B) via cyclodehydration of IIId,f and VIII(R = H)

Solution of acid (300 mg) in dry pyridine (3 ml) were treated with acetic anhydride (3 ml) at room temperature when intense yellow colour developed. The reaction mixture was briefly warmed on a steam-bath, cooled and diluted with enough ether. Separated product was collected, thoroughly washed with dry ether, dried and finally crystallised.

Vd : deep yellow silky needles (MeCN), m.p. 200-201 (d), identical (TLC, IR, m.m.p.) with that isolated from perchlorate salt (IVd).

Vf: yellow needles (acetone), m.p. 213-14°(d); yield 34% (based on ester IIf); R_f 0.28; UV(MeCN): 226(8,795), 273(11,290), 323(8,928), 410(4,725); 410 band shifted to 426 nm in benzene; yellow MeCN

solution also became colourless on protonation; IR: 3260, 3090(N−H), 1678w(C=O, polar), 1630s(C=O, amide); MS: *m/z* (rel. intensity): 273(76.4, M^+), 206(100), 157(8.8, 6-amino-3-methyl-2-thiopyrimidine-4-one), 124(55, 157−SH), 121(60, $Ph.CS^+$), 83(70, 124−CH_3CN) and 68(28.83−Me) (Found: C, 56.9; H, 4.2; S, 11.5. $C_{13}H_{11}N_3O_2S$ requires C, 57.1; H, 4.0; S, 11.7%).

IX: yellow needles (acetone - pet.ether), m.p. 187-88°(d); yield 44%; highly sensitive to organic solvents with rapid loss of yellow colour even at room temperature; UV(qualitative, MeCN): 227, 283, 434; 434 band shifted to 459nm in benzene; IR: 1715(C=O, polar), 1615(C=O, amide).

Acylation of IVd and isolation of mesoionic ketones (Vg)

To an ice-cold suspension of IVd(500 mg) in dichloromethane (10 ml) containing benzoyl- or *p*-nitrobenzoyl chloride (2.2 equiv) a solution of triethylamine (3 equiv) in the same solvent(5 ml) was added dropwise with stirring during 30 min. After further stirring for 1 hr, the mixture was washed thoroughly with water, dried, the solvent distilled off and the residue triturated with MeCN to afford orange yellow solids which were crystallised.

Vg(Ar=Ph): orange yellow needles (MeCN), m.p. 204-5°(d); R_f 0.56; yield 44%; UV(MeCN): 245(17,000), 370(13,800); IR: 1710-1700br (C=O, polar), 1630 (C=O, amide) (Found: C, 59.9; H, 4.0; S, 10.4. $C_{15}H_{12}N_2O_3S$ requires C, 60.0; H, 4.0; S, 10.7%).

Vg(Ar=*p*−NO_2Ph): deep yellow silky needles (acetone), m.p. 197-98°(d); R_f 0.60; yield 72%; spraingly soluble in common organic solvents. UV(qualitative, MeCN): 217, 260 & 385; and the band at 385 shifted to 393 nm in benzene. IR: 1720(C=O, polar) & 1705(C=O); MS, *m/z* (rel intensity): 345(100, M^+), 156(20, thione, cf. Vd), 150(40, *p*-NO_2.Ph.CO^+), 123(55, 156−SH), 83(30, 123−Me.C ≡ CH), 68(14,83−Me); (Found: C, 52.1; H, 3.1; S, 9.3. $C_{15}H_{11}N_3O_5S$ requires C, 52.2; H, 3.2; S, 9.3%).

Mesoionic azo-derivatives (VI)

To an ice-cold solution of perchlorate salt (IV, 250 mg) in ethanol (7.5 ml) was added with stirring, a clear ice cold solution of the aryldiazonium chloride (from 1 equiv arylamine) in minimum amount of water. To the above was added in one lot a clear solution of sodium acetate (5 equiv) in minimum amount of water. Deep red crystalline material which separated out immediately was collected after 15 min, washed with water, dil.aq $NaHCO_3$, water, ethanol, ether and dried at room temperature *in vacuo*.

VIa(Ar=*p*-MePh): sparingly soluble dark red material, m.p. 132-33°(d); yield 98% UV(qualitative, MeCN): 226, 240, 375, 475; IR: 1700w (C=O, polar), 1650(br, C=O); MS: *m/z* (rel intensity): 142(30, 3-methyl-2-thiopyrimidine-4-one), 119(100, Me.Ph.N=N^+), 109(40, 142−SH), 91(25, 119−N_2), 83(50, 109−CH≡CH), 68(20, 83−Me) (Found: C, 56.2; H, 3.9; S, 10.2. $C_{14}H_{12}N_4O_2S$ requires C, 56.0; H, 4.0; S, 10.7%).

VIc(Ar = *p*-Cl.Ph): sparingly soluble dark red crystals, m.p. 174-75°(d); yield 25%; UV(qualitative, MeCN): 222, 255sh, 375, 460; band at 460 shifted to 470 nm in benzene; IR: 1695s(C=O, polar), 1650w(C=O) (Found: C, 57.2; H, 4.3; S, 10.1. $C_{15}H_{14}N_4O_2S$ requires C, 57.3; H, 4.5; S, 10.2%).

VIc(Ar = *p*-ClPh): sparingly soluble dark red crystals, m.p. 189-90°(d); yield 37%; UV(qualitative, MeCN): 223, 250, 256, 380, 462; band at 462 shifted to 472 nm in benzene; IR: 1710s(C=O, polar), 1640w(C=O) (Found: C, 50.2; H, 3.3; S, 9.5. $C_{14}H_{12}ClN_4O_2S$ requires C, 50.2; H, 3.3; S, 9.6%).

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Reactions of a Chalcone with Hydroxylamine

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2′-Hydroxy-4-methoxy-5′-methylchalcone (**1**) with hydroxylamine hydrochloride in dil. AcOH gives 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-Δ^2-isoxazoline (**2**) instead of 2′-hydroxy-4-methoxy-5′-methylchalcone oxime (HMMCO, **3**) as reported by earlier workers. Compound **1** on refluxing with hydroxylamine hydrochloride in pyridine gives 4′-methoxy-6-methylflavanone oxime (**5**) also obtainable from 4′-methoxy-6-methylflavanone (**4**) by oximation in dil. AcOH. However, **1** with hydroxylamine hydrochloride in the presence of calculated amount of sodium hydroxide, pyridine or sodium acetate in ethanol furnishes 1-(2-hydroxy-5-methylphenyl)-3-hydroxylamino-3-(4-methoxyphenyl)propan-1-one (**6**) alongwith **3**. Compound **3** is isolable in a major amount in the presence of moist $NaHCO_3$ in benzene medium while strongly alkaline medium gives **6** and 1-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-ol (**8**), and with ethanolic sodium bicarbonate 3-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-1-propen-1-ol (**7**) is obtained. The products **3**, **6**, **7** and **8** were missed by previous workers while **2** and **5** were wrongly reported as **3** and **2** respectively. 2′-Hydroxy-5′-methylchacone also gives similar results. The structures have been established by chemical studies and spectral data(UV. IR and PMR).

Reaction of 2′-hydroxychalcones with hydroxylamine hydrochloride has been reported to give 3,5-diaryl-Δ^2-isoxazolines in ethanolic sodium hydroxide[1], pyridine[2-5], ethylenediamine[6] or sodium ethoxide[7]; flavanone oximes in ethanolic sodium bicarbonate[8,9]; oximinohydroxylamines in alkaline[10,11] or pyridine medium[12]; isoxazoles[10,11]; and addition products of NH_2OH to ethylenic bond of chalcones[13]. Interestingly in acid medium the formation of chalcone oximes has been reported by some workers[14,15] while the other school[16] has claimed the formation of isomeric isoxazolines.

Further, contradictory views appear in the literature regarding the assignment of structures to different products of the reaction. Aziz *et al.*[16] isolated two products, and suggested a structure similar to **2** to the product of low m.p. and a structure similar to **10** (isomeric isoxazoline) to the other product of high m.p.. Other workers[6,14,17] isolated a high melting product suggesting its structure similar to **2**.

In the present study we have investigated in a systematic way the reaction of **1** with hydroxylamine hydrochloride in different media such as dil. AcOH, pyridine, ethanol containing a few drops of HCl, calculated quantity of NaOH, pyridine or sodium acetate in ethanol, moist sodium bicarbonate in benzene or ethanol and excess of KOH in methanol. The results have been thoroughly discussed in this paper. The structural controversies in literature have been corrected by suggesting proper structures to different isolable products on the basis of spectral (UV, IR and PMR) and chemical evidences.

Compound **1** on refluxing with hydroxylamine hydrochloride in dil. acetic acid for 4 hr formed **2**.The PMR spectrum of **2** displayed an *ABX* pattern of Δ^2-isoxazoline ring[16]. The IR spectrum indicated intramolecular hydrogen bonding. Compound **2** remained unchanged on heating at 190° for 3 hr or on refluxing in pyridine for 4 hr or on refluxing with selenium dioxide in dioxane for 16 hr, but formed a monoacetate (**9**). The IR spectrum of **9** showed no νO-H indicating the presence of only one OH group in **2**. This suggested the structure of **2** as 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-Δ^2-isoxazoline. The proposed formation of 2′-hydroxy-4-methoxy-5′-methylchalcone oxime [HMMCO, (**3**)] under identical conditions by earlier workers[14,18,19] has therefore been ruled out. A closer examination of the isomers of Δ^2-isoxazoline (**2** and **10**) indicates that the hydrogen bond should be stronger in **2** than in **10** as planarity is attainable only in **2**. The comparison of IR and UV spectra also supported the structure **2**. The formation of **2** was also substantiated by its synthesis from 4′-methoxy-6-methylflavanone (**4**) by the action of hydroxylamine hydrochloride in acetic acid.

Compound **1** on refluxing with hydroxylamine hydrochloride in pyridine for 5 hr afforded 4′-methoxy-6-methylflavanone oxime (**5**) which could also be obtained from **4** by heating with hydroxylamine hydrochloride in AcOH for 5 min. The PMR spectrum of **5** exhibited an *ABX* pattern similar

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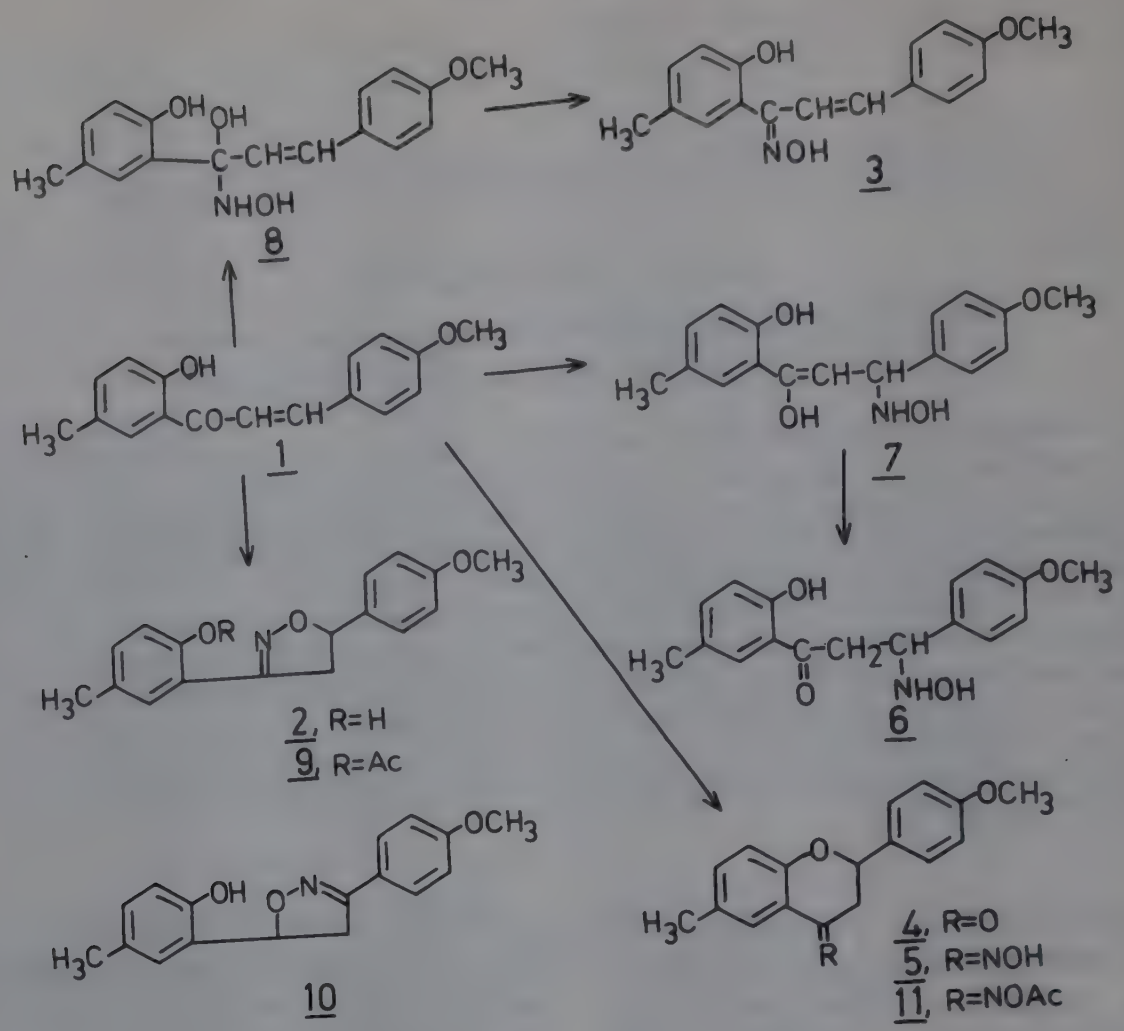

to that shown by **4**. Deoximation of **5** by boiling with conc. HCl or with chromium trioxide in AcOH gave back **4**. Acetylation of **5** gave N-acetoxy-4′-methoxy-6-methylflavanone oxime (**11**). Thus, compound **5** was identified as 4′-methoxy-6-methylflavanone oxime ruling out the structure **2** proposed by previous workers[6,14,19]. Witczak[21] has also reported similar results from flavanone.

Compound **1** on refluxing with $NH_2OH.HCl$ in ethanol containing a few drops of HCl for 6 hr gave **4** instead of reported[16] isoxazoline.

Treatment of **1** with $NH_2OH.HCl$ in the presence of a calculated amount of sodium hydroxide, pyridine or sodium acetate in ethanol gave 1-(2-hydroxy-5-methylphenyl)-3-hydroxylamino-3-(4-methoxyphenyl)propan-1-one (**6**) alongwith 2′-hydroxy-4-methoxy-5′-methylchalcone oxime (**3**). These products remained unchanged on refluxing in pyridine for 4 hr. Compound **3** underwent deoximation on boiling with HCl for 15 min or on exposure to atmosphere for 7 days giving back **1**.

With $NH_2OH.HCl$ in the presence of moist sodium bicarbonate in benzene, **1** gave **3** as a major product. However, **1** with sodium bicarbonate in ethanol gave 3-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-1-propen-1-ol (**7**).

Compound **1** with $NH_2OH.HCl$ in the presence of KOH in methanol gave **6** alongwith 1-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-ol (**8**). The structures of **3**, **6**, **7** and **8** were assigned on the basis of elemental analyses and spectral data.

Similar results except the formation of isoxazoline were obtained with 2′-hydroxy-5′-methylchalcone.

The reaction probably proceeds either by 1,2- or 1,4-addition. Both pathways compete in chalcones and the final product depends upon the reaction conditions. In nearly neutral media, both these reactions occur simultaneously forming a mixture of **3** and **6**. In benzene, the reaction follows 1,2-addition forming **5** only, while in strongly alkaline medium the isolation of **8** becomes possible because it fails to undergo dehydration to give **3**. The reaction in the presence of sodium bicarbonate in ethanol leads to **7**. The formation of **5** from **1** in pyridine can be considered to proceed through the isomerization of **1** to **4**. The flavanone formed by reversible isomerization of chalcone is removed by fast oximation to flavanone oxime **5** thereby shifting the equilibrium to the product side.

Formation of **2** does not necessarily proceed through an intermediate oxime, its subsequent cyclization and rearrangement giving **2** as oxime once formed, undergoes deoximation with acids giving the original chalcone **1**. The possible route for **2** involves formation of the intermediate hydroxylamino compound **8** by cyclodehydration. The failure to obtain the corresponding isoxazoline from 2′-hydroxy-

5′-methylchalcone in acid medium has been attributed to its isomerization to flavanone which is rapidly converted into flavanone oxime.

Experimental Procedure

Melting points were determined on a Neolab melting point apparatus using open capillaries and are uncorrected. PMR spectra were recorded on a Varian XL-100A high resolution NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm), IR spectra in nujol on a Pye-Unicam SP2000 IR spectrophotometer (ν_{max} in cm^{-1}), and UV-VIS spectra in chloroform on an Aminco-Bowman DW 2A UV-VIS spectrophotometer (λ_{max} in nm). TLC was performed on silica gel-G layers (0.3 mm thick) using iodine vapours for visualization. The elemental analyses were carried out on a Coleman C, H analyser. The chalcones and flavanones were prepared by known methods[22,23].

Reaction of 2′*-hydroxy-*4*-methoxy-*5′*-methyl-chalcone* (1) *with hydroxylamine hydrochloride*:

(a) *In acetic acid*

To a solution of **1**(2.68 g, 10 mmol) in acetic acid(20 ml), was added a solution of hydroxylamine hydrochloride (1.4 g, 20 mmol) in water (5 ml) and the mixture refluxed for 4 hr and cooled to get 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-Δ^2-isoxazoline (**2**) (2 g, 70%) which crystallised from ethanol, m.p. 85°; R_f 0.87(benzene) (Found: C, 72.1; H, 6.0. $C_{17}H_{19}O_3N$ requires C, 72.1; H,6.0%); UV:278 and 320; IR:3160(intramolecularly H-bonded O-H), 1660(C=N), 950(−N−O), 900(νsC−O−N in 5-membred ring); PMR($CDCl_3$): 2.34(*s*,3H,Ar−C*H*$_3$), 3.88(*s*,3H,OC*H*$_3$), 3.45(*dd*, 1H, −C*H*H, *J*=18 and 8 Hz), 3.83(*dd*, 1H, −CH*H*, *J*=18 and 8 Hz), 5.68 (*dd*,1H, −C*H*, *J*=8 and 8 Hz),6.8-7.4(*m*,7H,Ar−*H*), 9.7(*s*,1H,OH); its ethanolic solution gave a dark green colour with ferric chloride; monoacetate:m.p. 88°, R_f 0.34 (benzene), did not give ferric reaction.

(b) *In pyridine*

To a solution of **1** (2.68 g, 10 mmol) in pyridine(20 ml), hydroxylamine hydrochloride (1.4 g, 20 mmol) was added and the mixture refluxed for 5 hr, cooled, treated with dil. AcOH (10%) and the product crystallised from ethanol to get 4′-methoxy-6-methylflavanone oxime (**5**) (1.2 g, 42%), m.p. 208°; R_f 0.36 (benzene) (Found:C,71.8;H,6.4. $C_{17}H_{19}O_3N$ requires C,72.1;H, 6.0%); UV: 308 and 329; IR: 3100-3300(O−H), 1660(C=N),1070 (νC−O−C in a 6-membered ring), 960(=N−O);PMR($CDCl_3$): 2.30 (*s*,3H,Ar−C*H*$_3$), 3.88(*s*,3H,OC*H*$_3$), 2.79(*dd*,1H, −C*H*H,*J*=18 and 14Hz), 3.54(*dd*,1H, −CH*H*, *J*=18 and 4Hz), 5.06(*dd*,1H, −C*H*,*J*=14 and 4Hz), 6.8-8.0(*m*, 7H,Ar−*H*), 1.62(*s*,1H,OH). On boiling with HCl for 20 min or with CrO_3 in AcOH at 80° for 3 hr it gave **4**. The acetylation of **5** gave N-acetoxy-4′-methoxy-6-methylflavanone oxime (**11**), m.p. 188°(Found:C,70.4; H,5.6. $C_{19}H_{19}O_4N$ requires C,70.1;H,5.8%).

(c) *In ethanol in the presence of a little conc. hydrochloric acid*

A mixture of **1** (2.68 g, 10 mmol), hydroxylamine hydrochloride (1.4 g, 20 mmol), ethanol (20 ml) and conc. HCl (0.5 ml) was refluxed for 6 hr and cooled. The separated product was crystallised from ethanol and identified as **5**(1.3 g, 46%).

(d) *In the presence of a calculated amount of sodium hydroxide in ethanol*

To a solution of **1** (2.68 g, 10 mmol) in ethanol (30 ml), a solution of hydroxylamine hydrochloride (1.4 g, 20 mmol) in cold aq. sodium hydroxide (10%, 6 ml, 15 mmol) was added and the reaction mixture refluxed for 15 min, poured in ice-cold water and acidified with HCl. The product separated was crystallised from benzene to give 1-(2-hydroxy-5-methylphenyl)-3-hydroxylamino-3-(4-methoxyphenyl)propan-1-one (**6**) (1.3g, 44%), m.p. 154°; R_f 0.45($CHCl_3-Et_2O$; 1:1) (Found:C,67.7;H,6.3. $C_{17}H_{19}O_4N$ requires C,67.8;H,6.3%); UV: 275 and 322; IR: 3420,3260,3180(O−H and N−H), 1640(C=O), 1310(N−C−H), 930(H−N−O); PMR($CDCl_3$ +DMSO-d_6): 2.28(*s*,3H,Ar−C*H*$_3$), 3.84(*s*,3H,OC*H*$_3$), 3.08 (*dd*, 1H, −C*H*H, *J*=14 and 5 Hz), 3.54 (*dd*, 1H, −CH*H*, *J*=14 and 8 Hz), 4.37 (*dd*, 1H, −C*H*, *J*=5 and 8 Hz), 5.0-6.5(*br*, 1H, NH), 6.6-7.5(*m*, 7H, Ar−*H*), 10-12 (*br*, 2H, OH); its ethanolic solution gave green colour with ferric chloride; remained unchanged on refluxing in pyridine for 4 hr; turned faint yellow on exposure to atmosphere. The mother liquor on addition of pet. ether gave 2′-hydroxy-4-methoxy-5′-methylchalcone oxime (**3**) (0.6 g, 21%), m.p. 66° (d); R_f 0.95(benzene); UV(ethanol): 262, 310 and 370; IR(KBr): 3400 (O−H), 1600-1640(C=N and C=C), 950(N−O) (Found: C, 72.1; H, 6.5. $C_{17}H_{17}O_3N$ requires C, 72.1; H, 6.0%), its ethanolic solution gave violet-blue colour with ferric chloride; remained unchanged on refluxing in pyridine for 4 hr and underwent deoximation giving **1** on refluxing with conc. HCl for 15 min or even on exposure to atmosphere for 7 days.

(e) *In the presence of calculated amount of pyridine in ethanol*

A mixture of **1** (2.68 g, 10 mmol), pyridine (1.6 ml, 20 mmol), hydroxylamine hydrochloride (1.75 g, 25

mmol) and ethanol (20 ml) was refluxed for 1 hr, cooled, poured in ice-cold water and the separated product crystallised from benzene to give **6** (1.5 g, 50%). Addition of pet. ether to mother liquor gave **3** (1.0 g, 35%).

(f) *In the presence of sodium acetate in ethanol*

A mixture of **1** (2.68 g, 10 mmol), sodium acetate (3 g), ethanol (20 ml), hydroxylamine hydrochloride (1.4 g, 20 mmol) and water (10 ml) was refluxed for 10 min, cooled, poured in ice-cold water and the separated product crystallised from benzene to give **6** (1.7 g, 57%). Addition of pet. ether to mother liquor gave **3** (0.6 g, 21%).

(g) *In the presence of moist sodium bicarbonate in benzene*

A mixture of **1** (2.68 g, 10 mmol), hydroxylamine hydrochloride (1.4 g, 20 mmol), sodium bicarbonate (1.7 g), water (1 ml) and benzene (20 ml) was refluxed for 1 hr, benzene layer separated while hot and solvent evaporated. The sticky product was worked up with benzene-pet. ether to give **3** (1.5 g, 53%).

(h) *In the presence of sodium bicarbonate in ethanol*

A mixture of **1** (2.68 g, 10 mmol), hydroxylamine hydrochloride (1.4 g, 20 mmol), sodium bicarbonate (3 g) and ethanol (30 ml) was refluxed for 6 hr and poured in water. The product separated was crystallised from ethanol to get 3-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-1-propen-1-ol (**7**) (1.1 g, 37%), m.p. 152° (d); R_f 0.16 ($CHCl_3$) (Found: C,67.8; H, 6.3. $C_{17}H_{19}O_4N$ requires C,67.8; H,6.3%); UV:284 and 322; IR: 3380, 3260-3240 (O−H and N−H), 1630(C=C), 1400(C−N), 940(O−NH), 840(C−H in trisubstituted alkene); PMR ($CDCl_3$ + DMSO-d_6): 2.26(*s*,3H,Ar−CH_3), 2.58(*s*,1H,−C$\overset{|}{H}$), 3.80(*s*,3H,OCH_3), 4.10(*s*,1H,−NH), 6.6-7.8(*m*,8H,Ar−*H* and =C$\overset{|}{H}$), 10.66(*s*,1H,OH),11.13 (*s*,1H,OH), 11.26(*s*,1H,OH); its ethanolic solution gave an intense green colour with ferric chloride.

(i) *In the presence of potassium hydroxide in methanol*

To a solution of **1** (2.68 g, 10 mmol) in methanol (50 ml), aq. solutions of hydroxylamine hydrochloride (1.4 g, 20 mmol in 2 ml) and KOH (3.75 g, in 10 ml) were added. The mixture was refluxed for 3 hr, cooled, acidified with dil. HCl and excess acid neutralised with sodium carbonate. The product separated was crystallised from ethanol to get 1-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-ol (**8**) (0.8 g, 27%), m.p. 145°; R_f 0.90(benzene) (Found:C,67.8; H,5.3. $C_{17}H_{19}O_4N$ requires C,67.8;H,6.3%); UV:290 and 311; IR:3420,3220, 3060-3020(N−H and O−H), 1630(C=C), 1410(C−N),1120 (C−O), 980(trans CH=CH), 950(C−NH); PMR($CDCl_3$): 2.40(*s*,3H,Ar−CH_3), 3.94(*s*,3H,OCH_3),6.8-8.0(*m*,9H,Ar−*H* and =C$\overset{|}{H}$), 9.44(*s*,1H,NH); its ethanolic solution gave an intense green colour with ferric chloride.

Similarly 2′-hydroxy-5′-methylchalcone was treated with hydroxylamine hydrochloride in different experimental conditions as described above. In dil. acetic acid or pyridine or ethanol in the presence of a little conc. HCl, it gave 6-methylflavanone oxime (51 and 48% respectively; m.p. 185°) whereas in the presence of a calculated amount of NaOH or pyridine or sodium acetate in ethanol, a mixture of 1-(2-hydroxy-5-methylphenyl)-3-hydroxyl- presence of sodium bicarbonate in ethanol, it afforded 3-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-phenyl-1-propen-1-ol (57%; m.p. 158°), and with potassium hydroxide in methanol it formed 1-hydroxylamino-1-(2-hydroxy-5-methylphenyl)-3-phenyl-2-propen-1-ol (26%; m.p. 147°).

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Synthesis & Mass Spectral Studies of Some 3-Alkyl-6-aryl-7-carbethoxy/carboxy-methyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines

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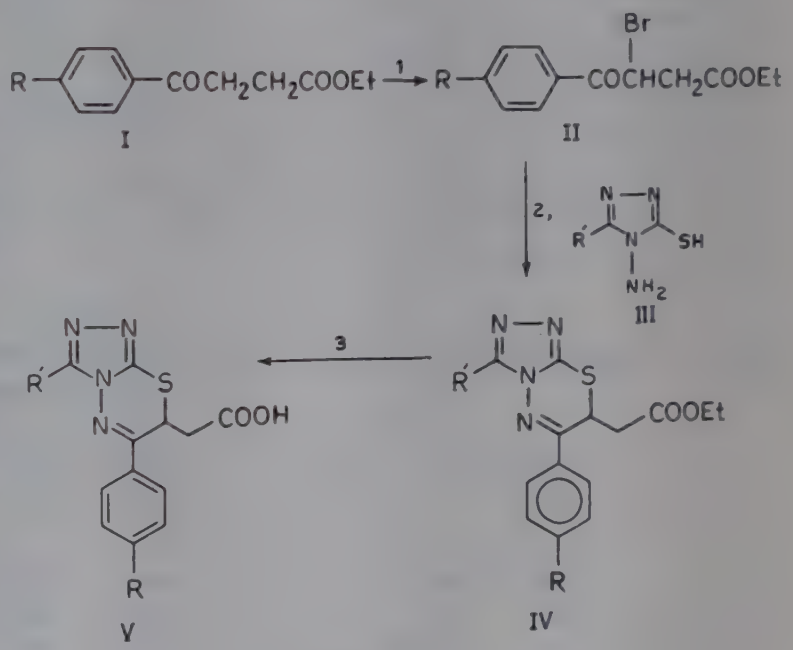
Several 3-alkyl-6-aryl-7-carbethoxymethyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (IV) have been synthesized by the condensation of appropriate ethyl *β*-aroyl-*β*-bromopropionates (II) with 4-amino-*s*-triazole-5-thiol (III, R′ = H) and its 3-methyl/ethyl analogues. Alkaline hydrolysis of IV gives the corresponding acids (V). The mass spectra of the esters (IV) show a unique fragmentation resulting in the concerted loss of CO_2 and C_2H_4 from the molecular ion through a rearrangement involving transfer of a hydrogen atom from ethyl group to the methylene carbon. The competing pathways involving the loss of $\dot{C}_2H_5$, $\dot{C}OOEt$ and $\dot{C}H_2COOEt$ radicals in the case of IV and $\dot{C}OOH$ and $\dot{C}H_2COOH$ radicals in the case of V from the molecular ions and thereafter cleavage of heterocyclic rings are also discussed.

During recent years considerable attention has been paid to the synthesis of condensed *s*-triazole heterocyclics. A survey of literature reveals that inspite of enormous literature reported[1-5] on the synthesis of triazolo[3,4-*b*][1,3,4]thiadiazine derivatives, there is no report on the mass spectra of this nucleus. In continuation of our work on heterocyclic compounds, it was therefore of interest to synthesize 3-alkyl-6-aryl-7-carbethoxy/carboxy-methyl-*s*-triazolo[3,4-*b*] [1,3,4]thiadiazines (IV & V) and analyse their mass spectra. In the present paper, we report the synthesis and mass spectral fragmentation of these compounds. The compounds were synthesized according to the reaction sequence delineated in Scheme 1.



Scheme 1

The required *β*-aroylpropionic acids were prepared by the Friedel-Crafts reaction of the respective aromatic compound and succinic anhydride[6-8]. Although *β*-aryoylpropionic acids were brominated directly and the bromoacids condensed with 3-alkyl-4-amino-*s*-triazole-5-thiols (III), it was observed in practice that they got partially esterified when the reaction was carried out in ethanol. Therefore, it was preferred to use the bromoethyl esters (II) instead of bromo acids in further study. Ethyl *β*-aroyl-propionates[9-11](I), obtained by estrification of keto acids, were brominated in $CHCl_3$ at methylene group adjoining the carbonyl group because of its higher activity as compared to the one adjacent to the ester group.

The PMR spectra of ethyl *β*-aroyl-*β*-bromo-propionates (II) due to some unusual features are of particular interest and worth mentioning. The PMR spectra of ethyl *β*-aroylpropionates (I) displayed the expected chemical shifts and the splitting patterns of the signals. However, the PMR spectra of II had a peculiar feature in that the two protons of the methylene group were not equivalent. The PMR spectrum of II (R = OCH_3) in $CDCl_3$ displayed signals at δ 1.25(*t*, 3H, $COOCH_2CH_3$), 3.05(*dd*, 1H, H-A, J_{AX} = 5.6 Hz and J_{AB} = 13.9 Hz, $COCHBrCH_2COOEt$), 3.48(*dd*, 1H, H-B, J_{BX} = 7.2 Hz and J_{AB} = 13.9 Hz, $COCHBrCH_2COOEt$), 3.85(*s*, 3H, OCH_3), 4.12(*q*, 2H, $COOCH_2CH_3$), 5.42(*dd*, 1H, H-X, J_{AX} = 5.6 Hz and J_{BX} = 7.2 Hz, $COCHBrCH_2COOEt$), 6.95(*d*, 2H,

aromatic protons at positions 3 and 5), 8.00 (*d*, 2H, aromatic protons at positions 2 and 6). The splitting of the signal for CH_2 protons into a pair of doublet of doublets and that of CHBr proton into a pair of doublets clearly fits into an *ABX* pattern. However, such an unequivalence of these methylene protons is not an altogether unexpected phenomenon. The only case reported in the literature is that of methyl 2,3-dibromo-2-methylpropionate where the methylene protons appear as a doublet of doublets rather than an expected singlet in the PMR spectrum[12].

Condensation of III with II proceeded smoothly in ethanol giving the required esters (IV; Table 1) which on subsequent hydrolysis with alkali in methanol gave the required acids (V; Table 1). The IR spectra of IV displayed an intense peak around 1730 due to C=O function whereas those of V were characterized by a peak at around 1700 (C=O) and a broad peak in the region 2400-2600 cm^{-1} (bonded OH). The PMR spectra of IV and V were also recorded. Apart from signals in the aromatic region, H-3 proton appeared as a sharp singlet at δ 8.65-8.80 whereas 3-methyl protons appeared as a singlet at 2.55-2.60 and 3-ethyl protons at triplet (3H) and quartet (2H) at 1.4 and 2.90 respectively. Methylene protons in both acids and esters appeared as a two-proton doublet at δ 2.55-2.75 and H-7 proton as a one-proton triplet at 4.80-4.90. In addition, the esters (IV) showed characteristic peaks at δ 1.25-1.30 (*t*) and at 4.15 (*q*).

The mass spectra of a large number of heterocyclic compounds have been reported from our laboratory in recent years[13-15]. In continuation of this work, the mass spectra of several members of the series IV and V were studied. The significant mass spectral data of a few of these compounds are listed in Table 2.

The predominant fragmentation in the mass spectrum of IVe involves expulsion of $\dot{C}_2H_5$, $\dot{C}OOEt$ and $\dot{C}H_2COOEt$ moieties from the molecular ion resulting in the formation of ions at *m/z* 321/323, 277/279 and 263/265 (Chart 1) respectively which further undergo fission via different competing pathways. The expulsion of COOEt is so facile that it forms the base peak. No ion corresponding to the fission of one or the other heterocyclic ring has been observed in the mass spectrum, rather heterocyclic rings suffer cleavage only after the expulsion of COOEt or CH_2COOEt moieties from the molecular ion demonstrating thereby that the expulsion of these moieties is energetically more favourable process than the fission of heterocyclic rings.

In a competing pathway concerted loss of CO_2 and C_2H_4 from the molecular ion through a hydrogen transfer rearrangement as shown in Chart 1 has also been observed. Further, evidence for the participation of ethyl group in this rearrangement was provided by the absence of $(M-72)^{\cdot}$ ion in the mass spectra of the corresponding acids (V). *p*-Chlorobenzyl cyanide (*m/z* 137.0002, Calc. for C_7H_4ClN, 137.0003) was

Table 1—Characterization Data of 3-Alkyl-6-aryl-7-carbetoxymethyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (IV) and the Corresponding Acids (V)

Compd	R	R′	m.p.* °C	Yield (%)	Mol. formula	N(%)†	
						Found	Calc.
IVa	H	H	100	59	$C_{14}H_{14}N_4O_2S$	18.8	18.5
IVb	Cl	H	138-39	65	$C_{14}H_{13}ClN_4O_2S$	16.7	16.6
IVc	OCH_3	H	109	60	$C_{15}H_{16}N_4O_3S$	16.7	16.9
IVd	H	CH_3	126	52	$C_{15}H_{16}N_4O_2S$	17.8	17.7
IVe	Cl	CH_3	159	60	$C_{15}H_{15}ClN_4O_2S$	16.0	16.0
IVf	OCH_3	CH_3	115	61	$C_{16}H_{18}N_4O_3S$	16.4	16.2
IVg	H	C_2H_5	133	57	$C_{16}H_{18}N_4O_2S$	17.2	17.0
IVh	Cl	C_2H_5	143	69	$C_{16}H_{17}ClN_4O_2S$	15.6	15.4
IVi	OCH_3	C_2H_5	121	50	$C_{17}H_{20}N_4O_3S$	15.6	15.6
Va	H	H	129	86	$C_{12}H_{10}N_4O_2S$	20.6	20.4
Vb	Cl	H	181	83	$C_{12}H_9ClN_4O_2S$	18.4	18.2
Vc	OCH_3	H	123	76	$C_{13}H_{12}N_4O_3S$	18.0	18.4
Vd	H	CH_3	149	79	$C_{13}H_{12}N_4O_2S$	19.5	19.4
Ve	Cl	CH_3	235	80	$C_{13}H_{11}ClN_4O_2S$	17.4	17.4
Vf	OCH_3	CH_3	132	80	$C_{14}H_{14}N_4O_3S$	17.4	17.6
Vg	H	C_2H_5	158	72	$C_{14}H_{14}N_4O_2S$	18.8	18.5
Vh	Cl	C_2H_5	199	85	$C_{14}H_{13}ClN_4O_2S$	16.6	16.6
Vi	OCH_3	C_2H_5	142	82	$C_{15}H_{16}N_4O_3S$	16.8	16.9

*Solvents used for crystallization were aq.ethanol for IVa-IVi and EtOH for Va-Vi
†Satisfactory C and H analyses were also obtained.

Table 2—Significant Mass Spectral Data of IV and V (Arranged to Display the Coincidence of Fragment Ions in Various Compounds) (Percentage Abundances are given in parentheses)

Sl	IVb	IVd	IVe	IVh	Ve	Vh
1	336/338 (51)	316 (85)	350.06032 (60)	364/366 (68)	322/324 (100)	336/338 (100)
2	307/309 (22)	287 (17)	321.02316 (10)	335/337 (12)	—	—
3	264/266 (21)	244 (26)	278.03658 (63)	292/294 (20)	—	—
4	263/265 (100)	243 (100)	277.03136 (100)	291/293 (100)	277/279 (47)	291/293 (37)
5	249/251 (33)	229 (25)	263.01584 (61)	277/279 (16)	263/265 (43)	277/279 (31)
6	—	211 (25)	245.06010 (18)	259/261 (18)	245/247 (10)	259/261 (9)
7	227 (44)	—	241.05570 (19)	255 (15)	241 (14)	255 (14)
8	—	174 (7)	207.99099 (8)	208/210 (5)	208/210 (10)	208/210 (10)
9	164/166 (42)	130 (32)	164.00223 (8)	164/166 (8)	164/166 (68)	164/166 (65)
10	127 (33)	141 (19)	141.02349 (7)	155 (10)	141 (35)	155 (57)
11	126 (22)	140 (12)	140.02845 (6)	154 (8)	140 (19)	154 (57)
12	137/139 (40)	103 (41)	137.00023 (10)	137/139 (5)	137/139 (32)	137/139 (34)
13	136/138 (69)	102 (64)	135.99634 (8)	136/138 (5)	136/138 (40)	136/138 (40)
14	112 (78)	126 (5)	126.01273 (8)	140 (5)	126 (6)	140 (21)
15	101 (40)	115 (90)	115.02138 (25)	129 (7)	115 (53)	129 (32)
16	94 (13)	108 (10)	108.05624 (15)	122 (7)	108 (12)	122 (10)
17	—	99 (54)	99.00186 (17)	99 (6)	99 (61)	99 (60)
18	73 (28)	87 (27)	87.01437 (8)	101 (6)	87 (18)	101 (34)

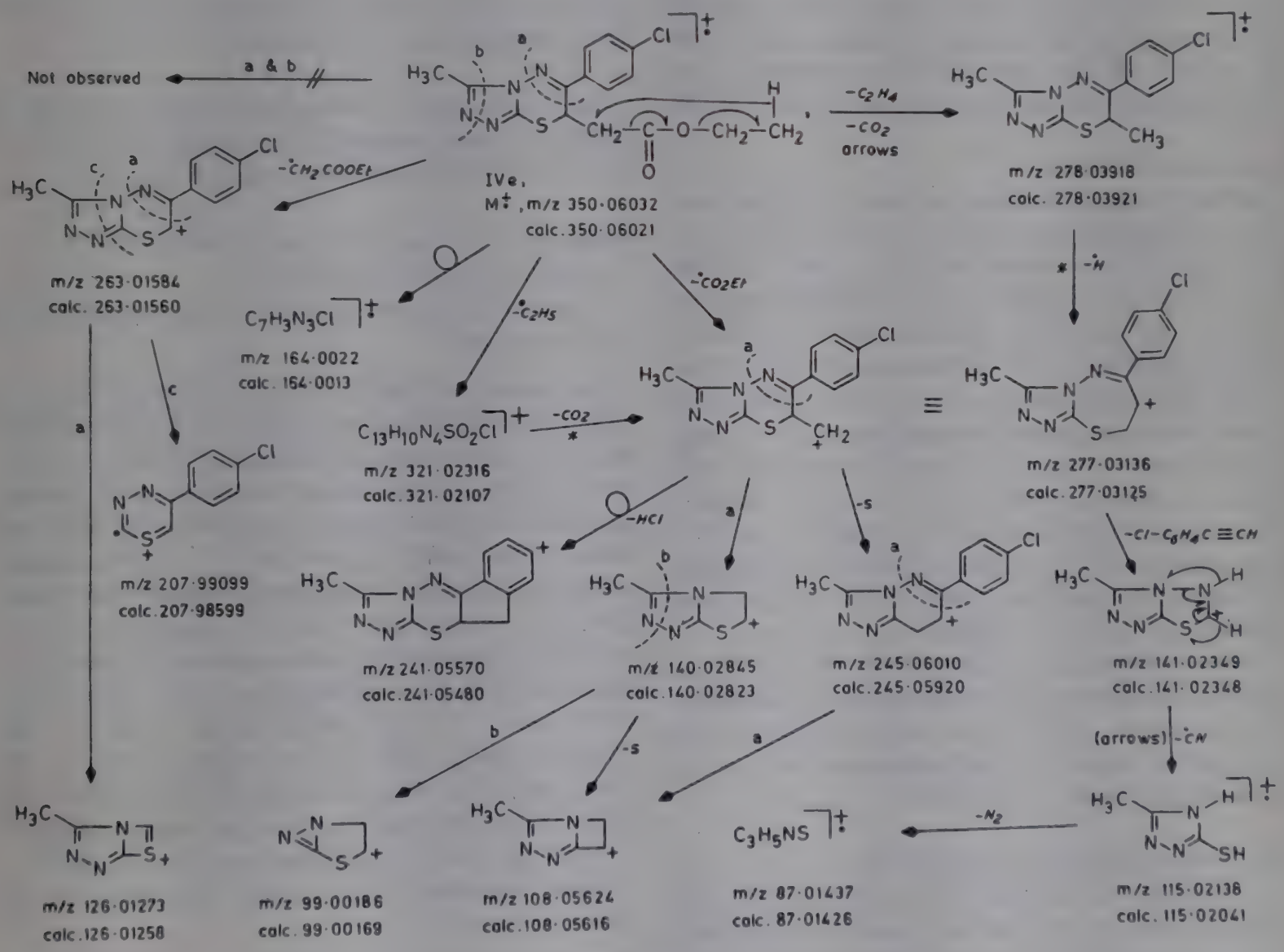


Chart 1

eliminated from the ions at *m/z* 263/265, 277/279 and 245/247 forming the ions at *m/z* 126, 140 and 108 respectively. The ion at *m/z* 141 formed by the elimination of *p*-chlorophenylacetylene from the ion at *m/z* 277/279 loses CN radical through hydrogen rearrangement to furnish 3-methyl-*s*-triazole-5-thiol

ion (*m/z* 115.02138. Calc. for $C_3H_4N_3S$ *m/z* 115.02042). All these and other related processes which were supported by accurate mass measurements of the fragment ions are shown in Chart 1 for the fragmentation of IVe, and were also observed in the mass spectra of IVb, IVd and IVh (Table 2).

Unlike the mass spectra of IV in which (M − 73) ion constitutes the base peak, the mass spectra of V show the molecular ion as the base peak. The molecular ion of V after loosing $\dot{C}OOH$ and $\dot{C}H_2COOH$ radicals undergoes fragmentation in identical manner as that of IV.

It is noteworthy that chlorine remains intact throughout (except IVd, R = H) with most of the fragment ions of IV as well as V. Substitution in the benzene ring appears to have little influence on various fragmentation pathways but substitution in the triazole ring by methyl or ethyl group has some influence on the fragmentation pattern. This is supported by the fact that the ions at *mz* 231/233 corresponding to the loss of sulphur atom from the ions at *m/z* 263/265 and those at *m/z* 208/210 and 99 corresponding to the rupture of triazole ring in the ions at *m/z* 249/251 and 140/142 respectively were conspicuously absent in the mass spectrum of IVb (R′ = H).

Experimental Procedure

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in nujol on a Beckman IR-20 spectrophotomer (ν_{max} in cm^{-1}), PMR spectra in $CDCl_3$ or DMSO-d_6 using TMS as internal standard on an R-32 Perkin-Elmer instrument (chemical shifts in δ, ppm) and mass spectra at 70 eV on an AEI MS-30 spectrometer fitted with a direct inlet system (source tempeerature being kept at 180°). High resolution measurements were made on a Kratos MS-50S instrument equipped with a 23 k gauss magnet. The running conditions were: source temperature 200°, electron energy 50 eV, resolution 8500 at 30 sec/decade. The sample was calibrated against PFK and data were collected on LOGOS 11/sigma 7 data system.

4-Amino-5-mercapto-*s*-triazole (III, R′ = H)[4] was prepared by heating thiocarbohydrazide with formic acid whereas its 3-methyl and ethyl analogues were prepared/ by heating thiocarbohydrazide with acetic and propionic acids respectively[2,3].

Ethyl β-aroyl-β-bromopropionates (II)

A solution of bromine (16 g, 0.1 mol) in dry chloroform (30 ml) was added gradually with stirring to a solution of ethyl β benzoylpropionate (I, R = H) (20.6 g, 0.1 mol) in dry chloroform (150 ml) containing anhyd. $AlCl_3$ (0.1 g) at 40 and guarded from moisture. The bromine colour disappeared rapidly with the evolution of HBr. The addition took 1 hr and the stirring was continued for another 30 min. The solvent was removed under reduced pressure and the residual thick liquid taken into ether, washed with 1% $NaHCO_3$ solution, then with water, dried (Na_2SO_4) and ether removed to give ethyl β-benzoyl-β-bromopropionate (IIa) as semi-solid (24 g, 84%). It was used as such as it tended to decompose even under reduced pressure. However, its purity was ascertained by TLC (single spot): IR; 1720 (CO of COOEt), 1670 (ketonic C=O); PMR ($CDCl_3$): 1.25 (*t*, 3H, $COOCH_2CH_3$), 3.10, 3.50 and 5.50 (*dd*, 1H each, *ABX* system), 4.15 (*q*, 2H, $COOCH_2CH_3$), 7.45-8.35 (*m*, 5H, Ar-H).

Following members of the series II were also prepared in a similar way:

Ethyl β-bromo-β- (4-chlorobenzoyl)propionate(IIb, R = Cl)—Thick semi-solid liquid, yield 76%; IR: 1725 (C=O of COOEt), 1675 (ketonic C=O); PMR ($CDCl_3$): 1.25 (*t*, 3H, $COOCH_2CH_3$), 3.05, 3.48 and 5.45 (*dd*, 1H each, *ABX* system), 4.15 (*q*, 2H, $COOCH_2CH_3$), 7.00 (*d*, 2H, aromatic protons at positions 3 and 5), 8.00 (*d*, 2H, aromatic protons at positions 2 and 6).

Ethyl β-bromo-β- (4-anisoyl)propionate (IIc, R = OCH_3)—Thick semi-solid liquid, yield 72%, IR: 1715 (C=O of COOEt), 1675 (ketonic C=O).

3-Alkyl-6-aryl-7-carbethoxymethyl-s-triazolo-[3,4-b] [1,3,4]thiadiazines (IV)

A typical procedure adopted for the preparation of IV is as follows:

To a solution of the thiol III (R′ = CH_3) (1.30 g, 0.01 mol) in ethanol (40 ml) was added IIb (3.20 g, 0.01 mol) and the reaction mixture refluxed for 24 hr on a water-bath, cooled and the solvent removed under reduced pressure. The gummy mass was washed with ether and treated with $NaHCO_3$ solution (2%). After keeping overnight, the solid was filtered, washed with water, dried and crystallized from aq. ethanol to give 7-carbethoxymethyl-6-(*p*-chlorophenyl)-3-methyl-*s* triazolo[3,4-*b*] [1,3,4]thiadiazine (IVe; Table 1), IR: 1730 (ester C=O); PMR($CDCl_3$): 1.25 (*t*, 3H, $COOCH_2CH_3$), 2.60 (*s*, 3H, CH_3), 2.70 (*d*, 2H CH_2COOEt), 4.15 (*q*, 2H, $COOCH_2CH_3$), 4.80 (*t*, 1H, H-7), 7.50 (*d*, 2H phenyl protons at positions 3 and 5), 7.96 (*d*, 2H, phenyl protons at positions 2 and 6).

Other members of the series, thus prepared, are given in Table 1.

3-Alkyl-6-aryl-7-carboxymethyl-s-triazolo[3,4-b] [1,3,4]thiadiazines (V)

A typical preparation is given below:

To a suspension of IVe (1.75 g, 0.02 mol) in NaOH solution (7%, 20 ml) was added methanol (20 ml) and

the mixture heated to reflux for 1 hr on a water-bath, cooled, filtered from any undissolved material and acidified with acetic acid. The product, thus separated, was filtered, washed with water, dried and crystallized from ethanol to give Ve (Table 1).

A similar method was used for the preparation of other members of the series and their characterization data are given in Table 1.

Acknowledgement

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Synthesis & Antiinflammatory Activity of Some 2-(4′-Butyl-3′,5′-dimethylpyrazol-1′-yl)-6-substituted-benzothiazoles & 4-Butyl-1-(6′-substituted-2′-benzothiazolyl)-3-methylpyrazol-5-ols

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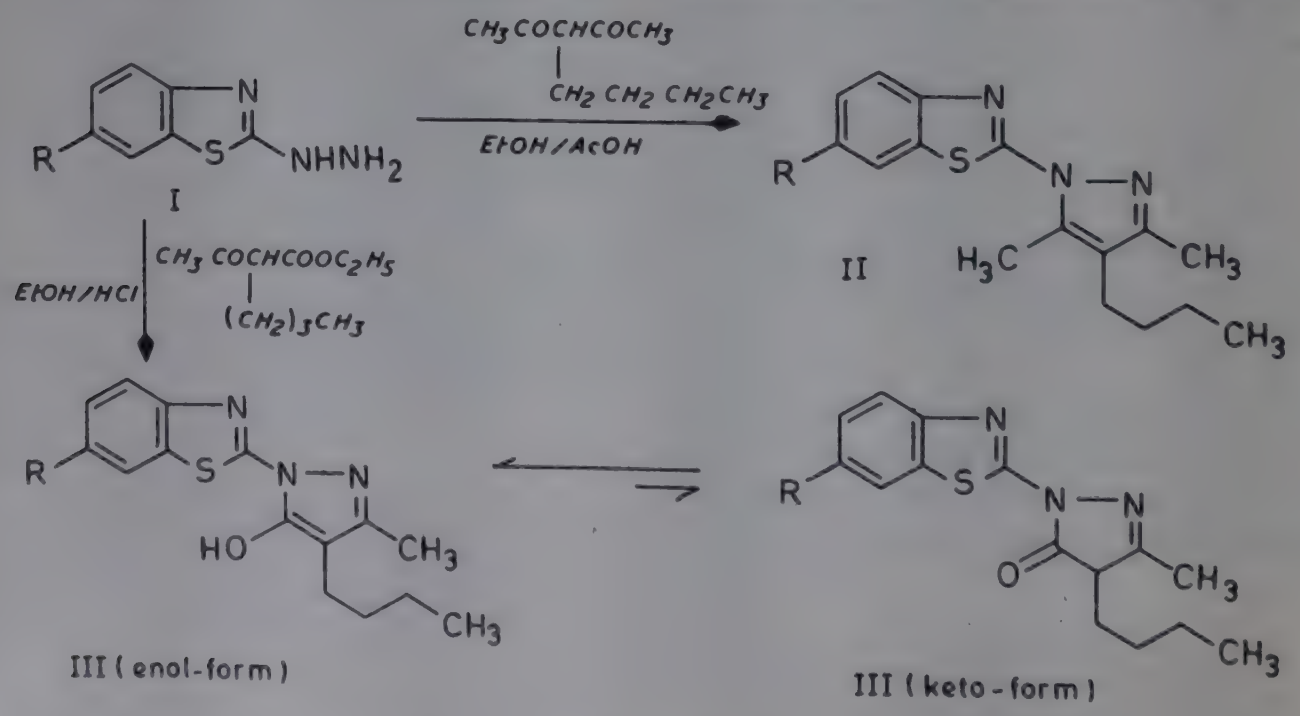
A number of title compounds (II and III) have been synthesized by the condensation of 6-substituted-2-hydrazinobenzothiazoles (I) with 3-butylpentane-2, 4-dione and ethyl α-(*n*-butyl)acetoacetate, respectively. Some of these compounds show significant antiinflammatory activity.

A number of benzothiazole derivatives recently synthesized in our laboratory have displayed antiinflammatory activity[1]. In view of the fact that phenylbutazone, the oldest and most thoroughly investigated antiinflammatory drug, possesses a butyl chain at position-4 of pyrazole nucleus[2], it was considered of interest to synthesize some benzothiazole derivatives bearing a 3, 5-dimethylpyrazolyl or 3-methylpyrazol-5-ol moiety with a butyl chain attached to position-4. The synthesis and antiinflammatory activity of such compounds (II and III) are reported in this paper.

6-Substituted-2-hydrazinobenzothiazoles (I)[3] on refluxing with 3-butylpentane-2, 4-dione[4] in ethanol in the presence of little acetic acid afforded 2-(4′-butyl-3′, 5′-dimethylpyrazol-1′-yl)-6-substituted-benzothiazoles (II; Scheme 1) in good yields. The characteristic features in the PMR spectra of II were the appearance of a seven-proton broad multiplet at δ 0.7-1.7 due to hydrogens of the butyl chain ($-CH_2CH_2CH_2CH_3$), a sharp singlet at 2.25 ascribed to the pyrazole 3-CH_3 protons, a two-proton triplet at 2.45 due to hydrogens of the butyl chain ($-CH_2CH_2CH_2CH_3$), a sharp singlet (3H) at 2.75 assignable to the protons of a methyl group at position-5 of the pyrazole ring and other signals which were in conformity with the structure II. The mass spectra of these compounds were also examined. While these spectra showed the molecular ion appearing prominently at the expected place, the base peak invariably arose by the loss of 43 mu from the molecular ion. Such a loss appeared quite interesting and we thought it worthwhile to investigate the process leading to its formation by high resolution mass spectrometry and linked scan data. Accurate mass measurement of this fragment ion established that it is generated by the loss of C_3H_7



I, II, III, a, R = H. b, R = CH_3. c, R = OCH_3. d, R = Cl. e, R = F.

Scheme 1

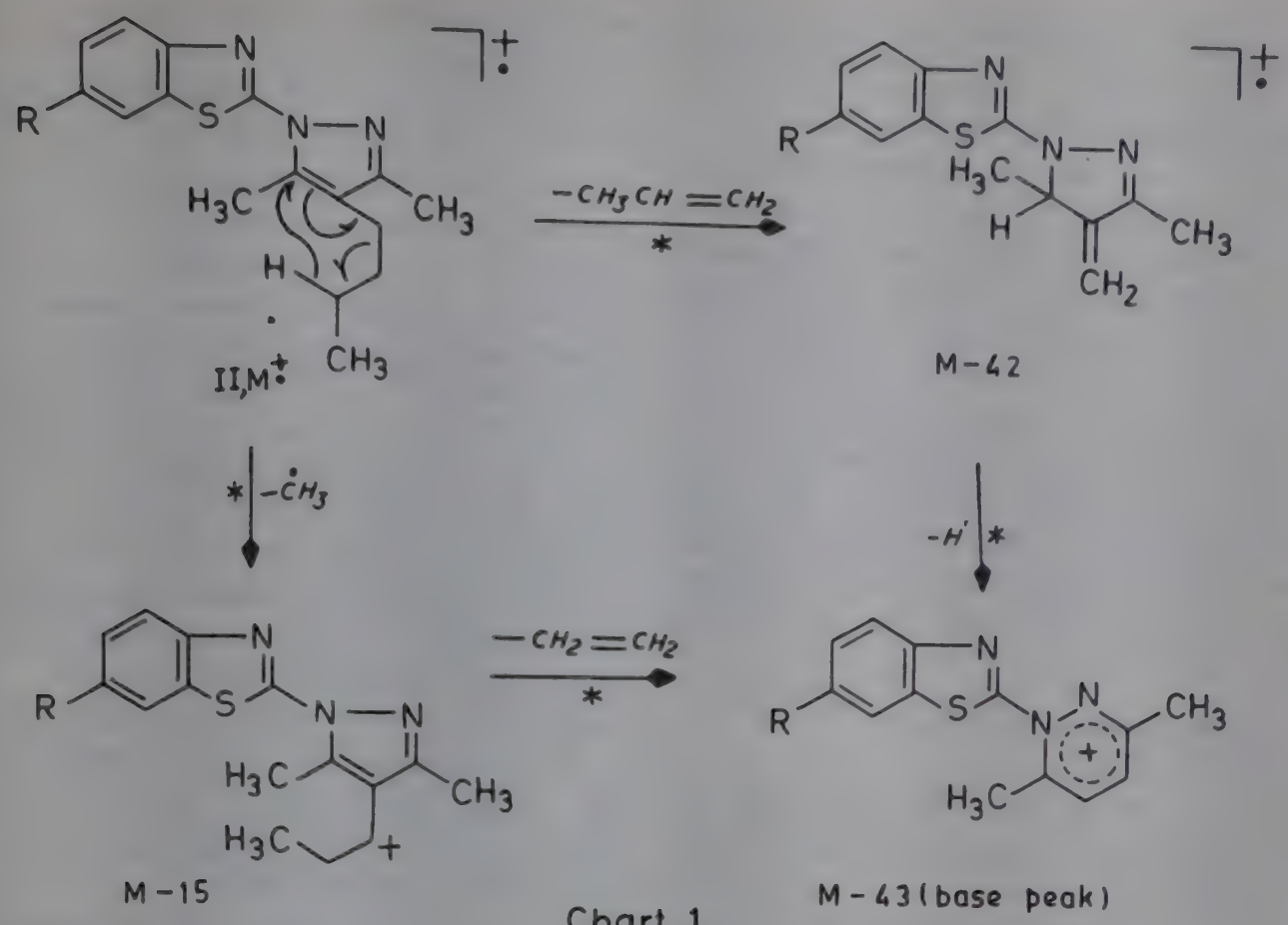


Chart 1

moiety from the molecular ion. An analysis of linked scan data suggested two modes for the formation of this fragment ion: (i) loss of methyl radical followed by ethylene molecule from the fragment ion, and (ii) loss of propene molecule through a rearrangement process followed by loss of hydrogen. These processes are shown in Chart 1 wherein the transitions supported by linked scan data are indicated by an asterisk.

Similar condensation of I with ethyl α-(*n*-butyl) acetoacetate[5] gave 4-butyl-1-(6′-substituted-2′-benzothiazolyl)-3-methylpyrazol-5-ols (III; Scheme 1). The enolic structure for compounds III was indicated by the absence of an IR absorption due to ring carbonyl and the presence of a strong absorption due to OH function in the region 3100-2800 cm^{-1}. This was confirmed by their PMR spectra. In addition to the seven protons belonging to the butyl chain and a three-proton singlet at δ 2.25 due to pyrazole 3-CH_3 group, there appeared a two-proton triplet at 2.38 due to protons of the carbon atom attached to the ring ($-CH_2CH_2CH_2CH_3$). As in the case of compounds II, the mass spectra of III were also characterized by the appearance of $(M-43)^+$ ion as the base peak. This process obviously involves the butyl side chain.

Biological screening

Selected compounds of the series II and III were subjected to preliminary testing for their antiinflammatory activity by carrageenin-induced rat paw edema test following the procedure of Winter *et al.*[6] and modified by Srimal and Dhawan[7]. The compounds were tested on mice at 0.2 of ALD_{50}. The standard used was phenylbutazone. The results are given in Table 1.

An examination of the results of Table 1 reveals that all the seven compounds belonging to the series II and III display significant antiinflammatory activity. Since no significant antiinflammatory activity was observed in the similarly constituted benzothiazole derivatives having an alkyl or carboxymethyl group attached to either a 3, 5-dimethylpyrazolyl[3] or 3-methylpyrazol-5-ol[8] moiety, it can be inferred that the presence of butyl chain plays a significant role in conferring the activity. The antiinflammatory activity of IIa is particularly impressive as not only this compound possess the highest activity (almost comparable to phenylbutazone), it is particularly nontoxic. Further investigations are to be carried out to establish the

Table 1—Antiinflammatory Activity of II and III

Compd	Inhibition of inflammation (%)	ALD_{50} (mg/kg i.p.)	Dose mg/kg p.o.
IIa	58	1000	200
IIb	30	121	24
IId	34	1000	200
IIIa	27	681	136
IIIb	42	147	30
IIId	49	464	92
IIIe	57	681	136
Phenyl-butazone	53	800	100

potential of this compound as an effective antiinflammatory agent.

Experimental Procedure

Melting points were taken in open capillaries and are uncorrected. IR spectra in nujol were recorded on a Beckman IR-20 spectrophotometer and PMR spectra (in $CDCl_3$, except IIIe) on an R-32 Perkin-Elmer (90 MHz) instrument (chemical shifts in δ, ppm). The mass spectra were scanned at 70 eV on Hitachi RMU-6D and Varian MAT-731 mass spectrometers. High resolution mass measurements and linked scan data were obtained on a JEOL JMS-D-X 300 mass spectrometer in conjunction with a JEOL, JMA 3100 data system at 70 eV, ionizing current 300 μA, accelerating voltage 30 kV and the ion source temperature 150°.

2-(4'-Butyl-3',5'-dimethylpyrazol-1'-yl)-6-chlorobenzothiazole (IId)

A mixture of Id (1.99 g, 0.01 mol) and 3-butylpentane-2, 4-dione (1.56 g, 0.01 mol) was refluxed for 3 hr in ethanol (30 ml) containing a few drops of acetic acid. After keeping the reaction mixture at room temperature for 6-8 hr, the separated solid was filtered, washed with water and crystallized from ethanol, m.p. 115°, yield 1.85 g (58%) (Found: N, 12.9. $C_{16}H_{18}N_3SCl$ requires N, 13.2%); PMR: 0.7-1.7 (*m*, 7H, $CH_2CH_2CH_2CH_3$), 2.25 (*s*, 3H, pyrazole 3-CH_3), 2.45 (*t*, $CH_2CH_2CH_2CH_3$), 2.75 (*s*, 3H, pyrazole 5-CH_3), 7.12-7.7 (*m*, 3H, Ar−H); MS: *m/z* 319.0896 (M^+) (Calc. for $C_{16}H_{18}N_3SCl$ 319.0907).

Other compounds were prepared similarly and crystallized from ethanol. Their characterization data are as follows:

IIa: m.p. 89° (yield 62%) (Found: N, 14.4. $C_{16}H_{19}N_3S$ requires N, 14.7%); PMR: 0.7-1.7 (*m*, 7H, $-CH_2CH_2CH_2CH_3$), 2.3 (*s*, 3H, pyrazole 3-CH_3), 2.45 (*t*, 2H, $-CH_2CH_2CH_2CH_3$), 2.75 (*s*, 3H, pyrazole 5-CH_3), 7.2-7.9 (*m*, 4H, Ar−H); MS: *m/z* 285 (M^+).

IIb: m.p. 110° (yield 64%) (Found: N, 14.0. $C_{17}H_{21}N_3S$ requires N, 14.0%); PMR: 0.7-1.7 (*m*, 7H, $CH_2CH_2CH_2CH_3$), 2.3 (*s*, 3H, pyrazole 3-CH_3), 2.4 (*t*, $-CH_2CH_2CH_2CH_3$), 2.5 (*s*, 3H, CH_3), 2.7 (*s*, 3H, pyrazole 5-CH_3), 7.3-7.9 (*m*, 3H, Ar−*H*); MS: *m/z* 299 (M^+).

IIc: m.p. 112° (yield 63%) (Found: N, 13.1. $C_{17}H_{21}N_3OS$ requires N, 13.3%); PMR: 0.7-1.7 (*m*, 7H, $CH_2CH_2CH_2CH_3$), 2.28 (*s*, 3H, pyrazole 5-CH_3), 2.4 (*t*, 2H, $CH_2CH_2CH_2CH_3$), 2.7 (*s*, 3H, pyrazole 5-CH_3), 3.90 (*s*, 3H, OCH_3), 6.9-7.8 (*m*, 3H, Ar−*H*).

IIe: m.p. 122° (yield 56%) (Found: N, 14.0. $C_{16}H_{18}FN_3S$ requires N, 13.9%); PMR: 0.7-1.7 (*m*, 7H, $CH_2CH_2CH_2CH_3$), 2.3 (*s*, 3H, pyrazole 3-CH_3), 2.4 (*t*, 2H, $CH_2CH_2CH_2CH_3$), 2.7 (*s*, 3H, pyrazole 5-CH_3), 7.25-7.8 (*m*, 3H, Ar−*H*).

4-Butyl-1-(6'-chloro-2'-benzothiazolyl)-3-methylpyrazol-5-ol (IIId)

To a solution of Id (1.99 g, 0.01 mol) in ethanol (60 ml) were added ethyl α-(*n*-butyl) acetoacetate (1.86 g, 0.01 mol) and a few drops of conc. HCl. The reaction mixture was refluxed for 5 hr, reduced to half and kept at room temperature overnight. The crystalline product was filtered, washed with a little ethanol and crystallized from ethanol, m.p. 132° (yield 56%) (Found: N, 13.1. $C_{15}H_{16}ClN_3OS$ requires, N, 13.1%); PMR: 0.7-1.7 (*m*, 7H, $CH_2CH_2CH_2CH_3$), 2.25 (*s*, 3H, pyrazole 3-CH_3), 2.38 (*t*, 2H, $CH_2CH_2CH_2CH_3$), 7.25-7.9 (*m*, 3H, Ar−*H*); MS: *m/z* 321.0696 (M^+) (Calc. for $C_{15}H_{16}N_3OSCl$ 321.0707).

Other members of this series were prepared similarly and crystallized from ethanol-acetic acid. Their characterization data are as follows:

IIIa: m.p. 103° (yield 68%) (Found: N, 14.2. $C_{15}H_{17}N_3OS$ requires N, 14.6%); PMR: 0.65-1.7 (*m*, 7H, $-CH_2CH_2CH_2CH_3$), 2.25 (*s*, 3H, pyrazole 3-CH_3), 2.4 (*t*, 2H, $-CH_2CH_2CH_2CH_3$), 7.2-8.0 (*m*, 4H, Ar−*H*); MS: *m/z* 287 (M^+).

IIIb: m.p. 98° (yield 72%) (Found: N, 14.0. $C_{16}H_{19}N_3OS$ requires N, 14.0%); PMR: 0.65-1.7 (*m*, 7H, $-CH_2CH_2CH_2CH_3$), 2.25 (*s*, 3H, pyrazole 3-CH_3), 2.4 (*t*, 2H, $-CH_2CH_2CH_2CH_3$), 2.5 (*s*, 3H, CH_3), 7.2-7.8 (*m*, 3H, Ar−*H*); MS: *m/z* 301 (M^+).

IIIc: m.p. 110° (yield 69%) (Found: N, 13.3. $C_{16}H_{19}N_3O_2S$ requires N, 13.2%).

IIIe: m.p. 124° (yield 62%) (Found: N, 13.9. $C_{15}H_{16}FN_3OS$ requires N, 13.8%); PMR (TFA): 0.8-1.8 (*m*, 7H, $CH_2CH_2CH_2CH_3$), 2.4 (*t*, 2H, $CH_2CH_2CH_2CH_3$), 2.45 (*s*, 3H, pyrazole 3-CH_3), 7.1-8.2 (*m*, 3H, Ar−*H*); MS: *m/z* 305 (M^+). O−*H* could not be located in the PMR spectra.

Acknowledgement

We are grateful to Dr K. Loening, Chemical Abstract Service, Columbus, Ohio, USA for providing nomenclature, Prof. A.L. Burlingame, Mass Spectrometry Resource, University of California, USA for providing mass spectra and to Dr T. Marunaka, Takishima, Japan for linked scan data. We also thank Prof. B.N. Dhawan and Dr R.C. Srimal, CDRI, Lucknow for biological testing, Chairman, Chemistry Department, Kurukshetra University, for providing facilities and the UGC, New Delhi for financial support.

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Notes

A New Synthesis of 5-Methyl-3-methylene-γ-butyrolactone

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An useful synthesis of 5-methyl-3-methylene-γ-butyrolactone (**6**) involving a Wittig-Horner reaction as a key step is described.

The α-methylene-γ-butyrolactone unit characterises a large group of sesquiterpenes known for their potential cytotoxic activity[1]. There has been a considerable spurt in developing synthetic routes to α-methylene-γ-lactones[2], because several biologically active natural products[3] have the α-methylene lactone moiety as an important structural feature. We report herein a useful and simple route (Scheme 1) to the synthesis of 5-methyl-3-methylene-γ-butyrolactone (**6**).

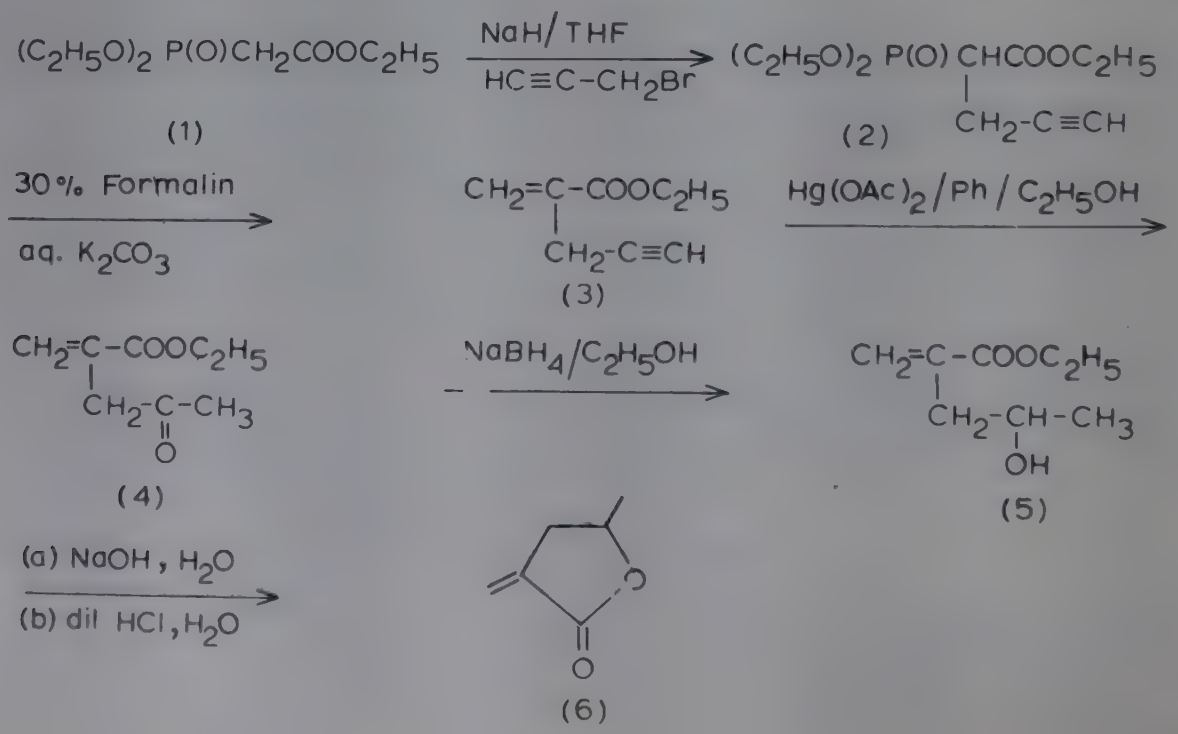
Alkylation of triethylphosphonoacetate (**1**) with propargyl bromide in the presence of NaH in THF at room temperature resulted in **2**, which when treated with 30% formalin in the presence of saturated aqueous potassium carbonate[4] gave ethyl α-propargylacrylate (**3**)[5] as a colourless liquid in 60% yield. Hydration of the acetylenic moiety in **3** using mercuric acetate, pyridine and ethanol under refluxing conditions gave **4** in 62% yield. Reduction of **4** using $NaBH_4$ in ethanol at room temperature gave the hydroxyester (**5**) in 76% yield which on lactonisation gave 5-methyl-3-methylene-γ-butyrolactone (**6**)[6] in 45% yield.

Alkylation of triethylphosphonoacetate (**1**) *with propargyl bromide: Alkylated product* (**2**)

To a slurry of 50% NaH (2.4 g, 0.1 mol) in dry THF (25 ml) was added dropwise with cooling, **1** (22.4 g, 0.1 mol) and stirred for 1 hr or until the gas evolution ceased. To this solution was added propargyl bromide (11.9 g, 0.1 mol) dissolved in dry THF (25 ml) slowly during 30 min, and then refluxed on a water-bath for 2 hr. The reaction mixture was cooled, filtered, the filtrate concentrated under reduced pressure and the residue distilled under reduced pressure to afford **2**; yield 17.6 g (71%); b.p. 106-109°/1 mm (Found: C, 50.1; H, 7.3. $C_{11}H_{19}O_5P$ requires C, 50.2; H, 7.2%); IR($CHCl_3$): 3300, 2120, 1730 cm^{-1}; PMR(CCl_4/TMS): δ 1.5 (*t*, 9H, 3 × Me), 2.1 (*d*, 2H, $-CH_2-$), 2.6 (*s*, 1H, $-C\equiv CH$), 3.0 (*s*, 1H, $-CH-$), 3.9-4.3 (*m*, 6H, 3 × O $-CH_2$).

Wittig-Horner reaction of **2**: *Formation of ethyl α-propargylacrylate* (**3**)

To a stirred mixture of **2** (2.63 g, 0.01 mol) and 30% aq. formalin (4 ml, 0.02 mol) was added slowly during 30 min at room temperature a saturated solution of potassium carbonate (2.8 g, 0.02 mol). At the end of the addition, the temperature reached 50-55 C and the stirring was continued for 1 hr more. Saturated ammonium chloride solution (40 ml) was added and the mixture thoroughly extracted with ether (4 × 100 ml). The combined organic phase was washed



Scheme 1

with brine, dried, the solvent removed under reduced pressure and the residual oil distilled under reduced pressure to afford **3**; yield 1.38 g (50%); b.p. 69-71° C/2 mm (Found: C, 69.1; H, 7.6. $C_8H_{10}O_2$ requires C, 69.6; H, 7.6%); IR($CHCl_3$): 3300, 2120, 1720, 1640 cm^{-1}; PMR(CCl_4/TMS): δ 1.3 (*t*, 3H, $-CH_3$), 2.2 (*s*, 1H, $-C\equiv CH$), 3.2 (*d*, 2H, $-CH_2$), 4.0-4.4 (*q*, 2H, $-OCH_2$), 6.0, 6.2 (*s*, 2H, $=CH_2$).

Hydration of **3** *to keto ester* (**4**)

A mixture of **3** (2.76 g, 0.02 mol), pyridine (10 ml), mercuric acetate (12.720 g, 0.04 mol) and ethanol (80 ml) was refluxed on a water-bath for 4 hr. After cooling, hydrogen sulphide was passed through the solution, the precipitated mercuric sulphide filtered off, the filtrate concentrated and the residue extracted with ether. The ether extract was successively washed with water, aq. sodium bicarbonate, water, dried, concentrated and distilled under reduced pressure to give pure **4**; yield 1.28 g (45%); b.p. 80-81°/1.5 mm (Found: C, 61.5; H, 7.7; $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%); IR($CHCl_3$); 1715(b), 1635 cm^{-1}; PMR(CCl_4/TMS): δ 1.35 (*t*, 3H, $-CH_3$), 2.15 (*s*, 3H, $-COCH_3$), 3.3 (*d*, 2H, $-CH_2-$), 4.0-4.4 (*q*, 2H, $-OCH_2-$), 6.1, 6.3 (*s*, 2H, $=CH_2$).

Reduction of **4** *to hydroxy ester* (**5**)

To an ice-cooled solution of **4** (3.120 g, 0.02 mol) in ethanol (25 ml), sodium borohydride (0.4 g, 0.01 mol) was added in portions during 20 min. Stirring was continued overnight at room temperature and the complex decomposed with gl. acetic acid. The solvent was removed under reduced pressure and to the residue water was added and extracted with chloroform. The organic layer was washed with brine, dried and concentrated to give **5** which was used as such in the next lactonization step.

Lactonization of **5**: *Formation of 5-methyl-3-methylene-γ-butyrolactone* (**6**)

Crude **5** was taken up in dil. aq. sodium hydroxide (30 ml) and stirred at room temperature for 4 hr. This solution was slowly added to excess of dil. hydrochloric acid (100 ml), stirred for 3 hr, thoroughly extracted with ether, the ether extract washed with water, brine and dried. Concentration of the extract gave **6**[6] as a viscous liquid; yield 2.25 g; IR(CCl_4): 1760, 1665 cm^{-1}; PMR(CCl_4/TMS): δ 1.3 (*d*, 3H), 2.2-3.6 (*m*, 2H), 4.5 (*s*, 1H, $-OCH$), 5.5 (*t*, 1H), 6.08 (*t*, 1H).

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A Short Synthesis of (2*S*)-2-Hydroxy-2-methylhexan-1-ol : A Useful Chiron for Synthesis of 15-Deoxy-16(*S*)-hydroxy-16-methylprostaglandins†

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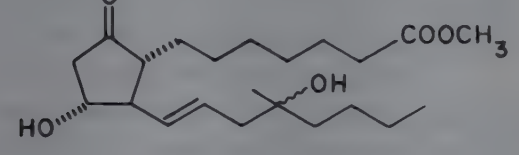
A short and simple synthesis of the title compound (VII) is described via asymmetric epoxidation of the allylic alcohol, 2-*n*-butyl-2-propen-1-ol (VIII).

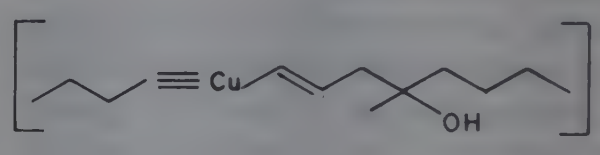
15-Deoxy-16-hydroxy-16-methylprostaglandin E_1 methyl ester (I) possesses considerably enhanced gastric antisecretory and antiulcer actions as compared to that of PGE_1, in which hydroxyl group is located at C-15. Also this molecular alteration confers oral activity, reduces the side effects and prolongs the biological actions of PGE_1[1,2]. All the four diastereomers of I have been prepared[3], but the gastric antisecretory activity is shown to solely reside in 16(*S*)-isomers.

Recemic I was first synthesised by Pappo and coworkers[4] via the stereospecific conjugate addition of the mixed cuprate (II) to the hydroxycyclopentenone (III). Although an asymmetric synthesis of (+)-III has been accomplished[5], (4*S*)-4-methyloct-1-yn-4-ol (IV), the precursor of II was prepared starting from chiral synthons, viz. (2*S*)-2-hydroxy-2-methylhexanoic acid[3] (V) or (*S*)-(+)-citramalic acid[6] (VI). The compound (V) in turn was obtained in low yield by chemical resolution and VI via biochemical transformations.

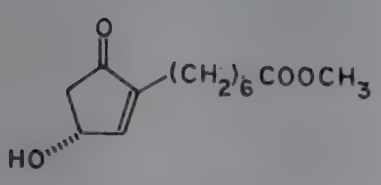
We now report a simple, asymmetric synthesis of the diol (2*S*)-2-hydroxy-2-methylhexan-1-ol (VII), the key intermediate which was already been transformed into IV. The essential step in the present synthesis involves asymmetric epoxidation of the allylic alcohol (VIII) under the conditions described by Sharpless *et al.*[7]. Since the tertiary chiral center of type VII is fairly widespread in nature, this may be a method of choice for the synthesis of such compounds.



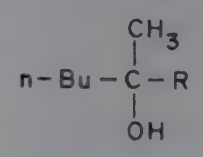
(I)



(II)

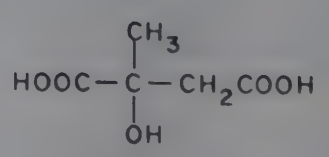


(III)

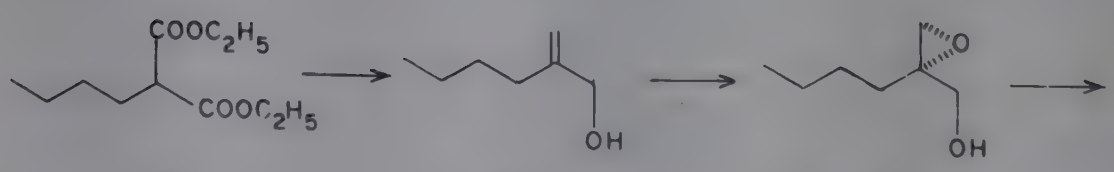


(IV) R = $CH_2C{\equiv}CH$

(+)-(V) R = COOH



(+) VI



(IX) (VIII) (−)-(X)

(S)-(−)-(VII)

†NCL Communication No. 3839.

The starting 2-*n*-butyl-2-propen-1-ol (VIII) was prepared by a one-pot synthesis involving treatment of ethyl 2-ethoxycarbonylhexanoate (IX) with sodium hydride followed by lithium aluminium hydride (LAH) in 1,2-dimethoxyethane (DME). The alcohol (VIII) on epoxidation with *t*-butyl hydroperoxide (TBHP) in the presence of an equimolar ratio of titanium isopropoxide and (+)-diethyl tartrate (DET) at $-23°$ using dichloromethane as solvent followed by dimethyl sulphide-sodium fluoride work-up gave[7] the epoxide (X) in 67% yield, $[\alpha]_D^{25} - 6.2°$ (*C*, 1, ether). The structure of X was in agreement with its spectral data (see preparation). Reductive cleavage of X with LAH in ether at room temperature gave VII, $[\alpha]_D^{25} - 3.8°$ (*C*, 1, chloroform) (lit. $[\alpha]_D^{25} - 4°$ (ref. 3) and $[\alpha]_D^{25} - 3°$ (ref. 6).

The PMR spectra were recorded on a Varian T-60 or Varian FT-80A spectrometer with TMS as internal standard and IR spectra on a Perkin-Elmer infracord model 683 spectrophotometer. Optical rotations were measured on a JASCO DIP 181 polarimeter.

2-n-Butyl-2-propen-1-ol (VIII)

Ethyl 2-ethoxycarbonylhexanoate (12.4 g, 0.064 mol) in DME (100 ml) was added dropwise during 2 hr to a stirred mixture of pre-washed sodium hydride (50% suspension, 4.2 g, 0.88 mol) in DME (25 ml). The reaction mixture was refluxed for 4 hr, cooled to 0° and LAH (7.6 g, 0.24 mol) added in portions during 20 min. It was allowed to stir at room temperature for 12 hr, cooled to 0° and ether (100 ml), water (10 ml) and aq. sodium hydroxide (5%, 25 ml) added sequentially.

The separated solid was filtered and washed with ether. The combined ether layer was washed with brine, dried (Na_2SO_4)), the solvent removed and the residue distilled under reduced pressure to give VIII as a colourless oil (5.8 g, 80%), b.p. 55-58°/10 mm (Found: C, 73.4; H, 12.3. $C_7H_{14}O$ requires C, 73.7; H, 12.3%); GC (ov 101, 120°): Rt 1.53 (98.16%); IR (neat): 1665, 3350 cm^{-1}; PMR (CCl_4): δ 0.9 (dist *t*, $J = 7$ Hz, 3H, H-6), 1.07-1.53 (*m*, 4H, H-4 & H-5), 2.0 (dist *t*, $J = 7$ Hz, 2H, H-3), 3.3 (*bs*, 1H, OH, exchangeable with D_2O), 3.9 (*bs*, 1H, H-1), 4.67 and 4.86 (each *bs*, each 1H, olefinic).

Epoxyalcohol (X)

A solution of (+)-diethyl tartrate (12.36 g, 0.06 mol) in dichloromethane (350 ml) was chilled to $-23°$ and to this were added, with stirring titanium isopropoxide (14.2 g, 0.05 mol), VIII (5.7 g, 0.05 mol) and *t*-butyl hydroperoxide (4.8 *N*, in CH_2Cl_2, 21 ml, 0.1 mol) sequentially and each at 5 min interval. Stirring was continued for further 30 min and mixture kept in a freezer at $-20°$ for 24 hr (progress of the reaction was followed by TLC). While maintaining the temperature at $-23°$, dimethyl sulphide (12.4 g, 0.2 mol) was added and the mixture stirred for 40 min. The cooled mixture was poured into aq. sodium fluoride (5%, 1 lit) and stirred at room temperature for 2 hr. It was filtered through sintered glass, organic layer separated and the aqueous layer washed with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), the solvent removed and the residue purified by column chromatography (silica gel) to give X as a colourless liquid (4.34 g, 67%) (Found: C, 64.3; H, 10.6. $C_7H_{14}O_2$ requires C, 64.2; H, 10.7%); GC (ov 101, 140°): Rt 1.56 (98.41%); IR (neat): 3420; PMR (CCl_4): δ 0.88 (dist *t*, $J = 7$ Hz, 3H, $-CH_3$), 1.36 (*m*, 6H, $2 \times -CH_2$), 1.92 (*bs*, 1H, OH, exchangeable with D_2O), 2.45, 2.88 (each *d*, $J = 4.8$ Hz, each 1H, oxirane protons) and 3.72 (*bs*, 2H, $-CH_2OH$); $[\alpha]_D^{25} - 6.2°$ (*C*, 1, ether).

2(S)-2-Hydroxy-2-methylhexan-1-ol (VII)

LAH (0.76 g, 0.02 mol) was added, with stirring to a cold solution of X (3.9 g, 0.03 mol) in ether (35 ml), stirred at room temperature for 12 hr, cooled to 0° and water (1 ml) and aq. sodium hydroxide (5%, 5 ml) were added. The separated solid was filtered, organic layer separated, washed with brine, dried (Na_2SO_4), solvent removed and the crude product purified by column chromatography (silica gel) to give VII as a colourless oil (3.7 g, 94%); GC (ov 101, 140°): Rt 1.61 (99%); IR (neat): 3360 cm^{-1}; PMR (CCl_4): δ 0.92 (dist *t*, $J = 7$ Hz, 3H, H-6), 1.16 (*s*, 3H, 2-CH_3), 1.4 (*m*, 6H, $3 \times -CH_2$), 2.24 (*bs*, 2H, $2 \times$ OH, exchangeable with D_2O) and 3.48 (*s*, 2H, H-1), $[\alpha]_D^{25} - 3.8°$ (*C*, 1, chloroform).

We thank Dr A V Rama Rao for valuable discussions.

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Synthesis of 4(*RS*), 8(*S*)-Dimethyldecanal: An Aggregation Pheromone of Red Flour Beetles†

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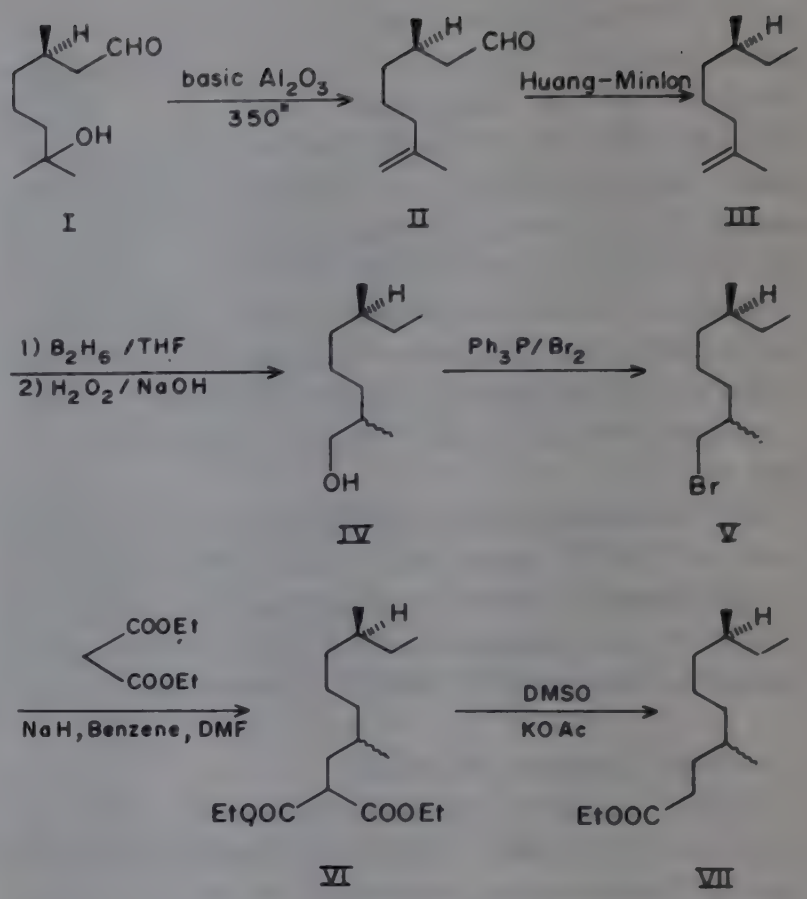
A simple and straight forward synthesis of the pheromone 4(*RS*), 8(*S*)-dimethyldecanal (IX) has been described starting from 7-hydroxycitronellal (I).

In 1980 T Suzuki, a Japanese worker, isolated and identified 4,8-dimethyldecanal as aggregation pheromone of red flour beetles, *Tribolium castaneum* and *T. confusum*[1]. Red flour beetles are known to be a serious pest infesting flour and meal of nearly all kinds of cereals.

We wish to report here an elegant, simple and straight forward synthesis of 4,8-dimethyldecanal (IX) from the inexpensive and abundantly available (+)-*R*-7-hydroxycitronellal (I) which contains most of the structural features of IX such as 8-carbon chain with methyl groups at appropriate places. The only task is to add two carbons to achieve the synthesis.

While the manuscript was under preparation a report by Mori *et al.*[2] appeared describing the absolute configuration of the natural pheromone at the two chiral centres as 4*R* and 8*R*.

7-Hydroxycitronellal on thermal dehydration on basic alumina at 350° following the reported procedure[3] gave rhodinal (II) along with other products. The reported Huang-Minlon method[3] was suitably modified for getting 2,6-dimethyloct-1-ene (III) from II in a high yield. The *in situ* hydroboration[4] of octene III in dry THF gave 2,6-dimethyloctan-1-ol (IV) in 92% yield, which on treatment with triphenylphosphine dibromide gave the corresponding bromide (V). Alkylation of diethyl malonate with V gave ethyl 2-carbethoxy-4,8-dimethyldecanoate (VI) in 80% yield. No alkylation was observed (TLC) by NaH in benzene even after 24 hr stirring at room temperature and 20 hr of refluxing. So, we optimised the condition of alkylation of diethyl malonate with V for (i) sure alkylation, (ii) higher yield, (iii) moderate conditions and (iv) to reduce yield or avoid the formation of unwanted possible dialkylated compound. By trying various mixtures of benzene and DMF, the ratio 1 : 1 was found to be the best suited one. No dialkylated product was formed in the reaction under the conditions empolyed. Decarbethoxylation of VI by the reported procedure[5] gave the ester VII in almost quantitative yield.



I II III IV V VI VII VIII IX

LAH reduction of VII and subsequent oxidation of the resulting alcohol (VIII) by Corey's reagent (PCC) gave 4(*RS*), 8(*S*)-dimethyldecanal (IX), $[\alpha]_D^{28} + 1°$ (*c*, 2.3, $CHCl_3$), identified by comparison of spectral data[2]. Considering the contribution due to chiral centre-4 as zero, the optical rotation of IX was in close agreement with that of *S* (+)-8-methyldecanal[6].

All b.ps are uncorrected, and unless otherwise stated these refer to bath temperatures. Extracts in organic solvents were dried over anhyd. Na_2SO_4. Optical rotations were recorded in chloroform on a Jasco DIP-181 digital polarimeter at wavelength 589 nm. IR (neat) spectra were recorded on a Perkin-Elmer infracord

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model 137-B spectrophotometer (ν_{max} in cm^{-1}), PMR spectra on a Varian T-60, FT-80 or WH-90 spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a CEC-2-110B double focussing spectrometer using direct inlet system. TLC analyses were carried out on glass plates coated with TLC grade (400-500 mesh) silical gel containing 13% $CaSO_4$ as binder. All the compounds gave satisfactory elemental analyses.

2,6-*Dimethyl*-1-*octene* (*III*)

Hydrazine hydrate (30 g) was added to a solution of II (46 g) in diethylene glycol (300 ml) and then KOH (52 g) added to it. The reaction mixture was refluxed for 2 hr, distilled and the distillate diluted with water and extracted with ether (100 ml × 3). The combined organic layer was washed with water, brine, dried and concentrated to give TLC-pure III, R_f 0.62 (pet. ether), yield 39 g (94%), b.p. 155°/714 mm (lit.[3] 163°/705 mm), $[\alpha]_D^{27}$ +6.8° (*c*, 1.8) (lit.[3] +6.5°); IR: 1645, 885 (C=CH_2) (lit.[3] 1640, 885); PMR (CCl_4): CCl_4 0.89 (6H, *m*, C_6- and C_7-CH_3), 1.1-1.44 (6H, *m*, methylene and methine protons), 1.66 (3H, *s*, vinyl methyl), 1.91 (2H, *m*, C_3-CH_2) and 4.6 (2H, *s*, C=CH_2).

2,6-*Dimethyloctan*-1-*ol* (*IV*)

To a stirred mixture of $NaBH_4$ (5 g), dry and peroxide-free THF (200 ml) and octene III (32 g), BF_3-Et_2O (20 ml) was added slowly during 4 hr under dry N_2 atmosphere. The reaction mixture was stirred for another 12 hr, and excess $NaBH_4$ destroyed by careful addition of water. To the alkylborane thus generated was added 3*N* aq. NaOH (100 ml) followed by dropwise addition of H_2O_2 (30%, 100 ml) during 5 hr maintaining the temperature at 25° throughout. Stirring was continued for 8 hr after which organic layer was separated. The aqueous layer was extracted with ether (100 ml × 3). The combined organic layer was washed with water, brine, dried and evaporated to get TLC-pure alcohol IV, (R_f 0.21) (benzene +1% ethyl acetate) yield 34 g (92%); IR: 3340 (−OH); PMR ($CDCl_3$): 0.8-1 (9H, *m*, 3×CH_3), 1-1.64 (10H, *brs*, methylene and methine protons) 2.91 (1H, *s*, −OH, exchangeable with D_2O) and 3.36 (2H, *d*, *J* = 5 Hz, CH_2OH); MS: *m/z* 158 (M^+).

1-*Bromo*-2,6-*dimethyloctane* (*V*)

To a stirred and cooled solution of Ph_3P (1.3 g) in dry CH_2Cl_2 (10 ml) under N_2, Br_2 (0.3 ml) in CCl_4 (3 ml) was added slowly, stirring continued for 30 min and then a solution of III (0.84 g) in CH_2Cl_2 (2 ml) added to it slowly. The reaction mixture was allowed to attain room temperature and left overnight. Excess of solvent was skipped off and the residue repeatedly extracted with hot pet. ether. Evaporation of pet. ether gave TLC-pure V, R_f 0.52 (benzene), yield 0.88 g (80%); PMR (CCl_4): 0.88-1 (9H, *m*, 3×CH_3), 1-1.72 (10H, *brs*, methylene and methine protons) and 3.31 (2H, *d*, *J* = 5 Hz, CH_2Br); MS: *m/z* 220, 222 (M^+).

Ethyl 2-*carbethoxy*-4,8-*dimethyldecanoate* (*VI*)

To a suspension of NaH (0.24 g) in benzene (10 ml) and DMF (10 ml) diethyl malonate (1.9 g) was added slowly with stirring under N_2 atmosphere and the stirring continued for 2 hr. The bromide V was then added to the above suspension and the reaction mixture heated in an oil-bath at 100° for 4 hr with stirring, cooled, diluted with water, organic layer separated and aq. layer extracted with benzene (20 ml × 2). Evaporation of benzene gave VI (2.1 g, 81%), (TLC, benzene, R_f 0.35), b.p. 135°/2 mm (bath); IR: 1735 (ester C=O); PMR ($CDCl_3$): 0.81 (9H, *brd*, 3×CH_3), 1.25 (16H, *brt*, 2×$COOCH_2CH_3$ and methylenes), 1.75 (2H, *m*, C_4- and C_8-H), 3.3 (1H, *t*, *J* = 5.5 Hz, C_2-H) and 4.16 (4H, *q*, *J* = 6 Hz, 2×$COOCH_2CH_3$).

Ethyl 4,8-*dimethyldecanoate* (*VII*)

A solution of VI (1.5 g) in DMSO (20 ml) containing KOAc (1.14 g) and H_2O (0.18 g) was refluxed for 6 hr, cooled and diluted with water. Extractive work-up gave VII (1.09 g, 98%), (TLC, benzene, R_f 0.44), b.p. 150°/10 mm (bath); IR: 1733 (ester C=O); PMR ($CDCl_3$): 0.86 (9H, *brs*, 3×CH_3), 1.1-1.74 (15H, *m*, $COOCH_2CH_3$, methylene and methine protons), 2.25 (2H, *t*, *J* = 6 Hz, C-2-CH_2) and 4.08 (2H, *q*, *J* = 6 Hz, $COOCH_2CH_3$).

4,8-*Dimethyldecan*-1-*ol* (*VIII*)

To a stirred and cooled suspension of LAH (0.38 g) in dry ether (75 ml), VII (2.2 g) in dry ether (10 ml) was added slowly during 30 min and left overnight. The reaction mixture was cooled and 1 ml H_2O and 1 ml 10% NaOH were added carefully followed by the addition of 3 ml of H_2O when a solid separated out. Ether was decanted and the residue extracted with ether (40 ml × 4). The combined ether layer was washed with water, brine, dried and evaporated to give TLC pure VIII, R_f 0.16 (benzene), yield 1.5 g, (88%); $[\alpha]_D^{28}$ +1.9° (*c*, 1.5); IR: 3330 (−OH); PMR ($CDCl_3$): 0.87 (9H, *m*, 3×CH_3), 1-1.65 (14H, *m*, methylene and methine protons), 1.75 (1H, *s*, −OH exchangeable with D_2O and 3.64 (2H, *t*, *J* = 5 Hz, CH_2OH); MS: *m/z* 186 (M^+).

4,8-*Dimethyldecanal* (*IX*)

To a suspension of PCC (1.8 g) in dry CH_2Cl_2 under nitrogen, a solution of VIII (0.5 g) in CH_2Cl_2 (2 ml) was added with stirring and stirring continued for 1 hr. Work-up of the reaction mixture gave IX (0.435 g, 88%)

$[\alpha]_D^{28} + 1°$ (*c*, 2.3); IR: 2700 (aldehyde), 1730 (C = O); PMR ($CDCl_3$): 0.75-0.87 (9H, *m*, $3 \times CH_3$), 1-1.78 (12H, *m*, methylene and methine protons), 2.28 (2H, *dt*, $J_1 = 1.8$ Hz, $J_2 = 6$Hz at C-2-CH_2) and 9.68 (1H, *t*, $J = 1.8$ Hz, CHO). Since the aldehyde IX was susceptible to autooxidation, it was converted into dimethyl acetal ($MeOH/H^+$, 0°, 24 hr); $[\alpha]_D^{25} + 0.7°$ (*c*, 1.7); IR: 1050, 1120, PMR ($CDCl_3$): 0.76-0.87 (9H, *m*, $3 \times CH_3$), 1.1-1.64 (14H, *m*, methylene and methine protons), 3.23 (6H, *s*, $2 \times -OCH_3$) and 4.25 [(1H, *t*, $J = 5$ Hz, $-CH(OMe)_2$].

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A Simple Synthesis of (±)-Combretastatin†

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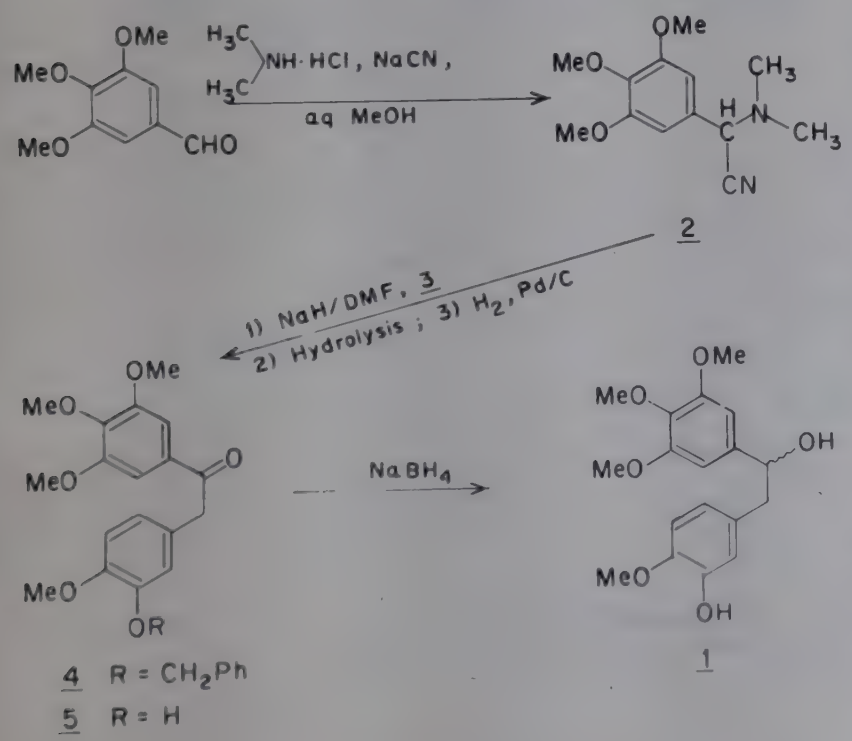
A simple synthesis of (±)-combretastatin (**1**) has been described starting from 3,4,5-trimethoxybenzaldehyde and isovanillin.

Earlier we have reported[1] the synthesis of combretastatin (**1**), a plant product[2] possessing central nervous system antineoplastic activity and being currently evaluated against several of National Cancer Institute's key evaluation systems. In this note we report yet another simple approach towards **1**.

An appropriately substituted deoxybenzoin, such as **4** is a key intermediate for the synthesis of **1**. Although many methods are known for the synthesis of deoxybenzoin, the method described by Dyke *et al.*[3] is very simple and useful. The desired deoxybenzoin (**4**) was prepared by C – C bond formation starting from 3,4,5-trimethoxybenzaldehyde and isovanillin (Scheme 1).

3,4,5-Trimethoxybenzaldehyde was treated with dimethylamine hydrochloride and sodium cyanide in aqueous MeOH to give the corresponding α-aminonitrile (**2**) in 96% yield. Isovanillin was converted into 3-benzyloxy-4-methoxybenzyl bromide (**3**)[1]. The alkylation of the anion of **2** with **3** followed by aqueous work-up directly gave the **4** in 75% yield. Catalytic hydrogenation of **4** over 10% Pd/C followed by reduction of the resulting **5** with $NaBH_4$ in ethanol gave (±)-combretastatin (**1**) in 90% yield, identical (co-IR in solution) with samples of natural and synthetic combretastatin[1].



SCHEME 1

N,N-Dimethyl-α-cyano-3,4,5-trimethoxybenzylamine (**2**)

3,4,5-Trimethoxybenzaldehyde (9.8 g, 50 mmol) in methanol (300 ml) was added during 1.5 hr to a solution of dimethylamine hydrochloride (4.9 g, 60 mmol) and sodium cyanide (2.94 g, 60 mmol) in water (30 ml). The mixture was stirred at room temperature for 5 hr, diluted with water (400 ml) and extracted with $CHCl_3$ (3 × 200 ml). After drying (Na_2SO_4) the combined $CHCl_3$ extract was evaporated and the residue crystallised from benzene pet-ether to give **2** as pale yellow needles (12 g) in 96% yield; m.p. 77°; IR 2200 cm^{-1} (C ≡ N); PMR (80 MHz, CCl_4): δ 2.27 [*s*, 6H, $-N(CH_3)_2$], 3.7 (*s*, 3H, OMe), 3.8 (*s*, 6*H*, 2 × OMe), 4.57 (*s*, 1H, –CH), 6.53 (*s*, 2H, Ar-H) (Found: C, 62.1; H, 7.4; N, 10.9. $C_{13}H_{18}O_3N_2$ requires C, 62.4; H, 7.2; N, 11.2%).

3′-Benzyloxy-3,4,5,4′-tetramethoxy-deoxybenzoin (**4**)

Sodium hydride (60% suspension in oil, 0.12 mmol) was washed with pet-ether and suspended in dry DMF (5 ml) under N_2. A solution of **2** (2.5 g, 10 mmol) in dry DMF (10 ml) was added and stirred under N_2 for 1 hr. To this was added a solution of 3-benzyloxy-4-methoxybenzyl bromide[1] (**3**, 3 g, 10 mmol) in DMF (10 ml) and stirred for 24 hr. The excess of NaH was destroyed with methanol (4 ml), diluted with water (50 ml) and stirred for 1 hr. It was extracted with benzene (3 × 75 ml). The combined extract was washed with water, dried (Na_2SO_4) and evaporated to give an oil which was purified by column chromatography (SiO_2, benzene-acetone) to give **4** (3.16 g) in 75% yield; IR: 1680 cm^{-1} (C = O); PMR (CCl_4): δ 3.7 (*s*, 12H, 4 × OMe), 3.86 (*s*, 2H, $-CO-CH_2$), 4.86 (*s*, 2H, $-OCH_2Ph$), 6.56 (*bs*, 3H, Ar-H), 7.0 (*s*, 2H, Ar-H), 7.16 (*bs*, 5H, aromatic) (Found: C, 70.9; H, 6.2. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.2%).

3′-Hydroxy-3,4,5,4′-tetramethoxydeoxybenzoin (**5**)

A solution of **4** (0.42 g) in EtOH (50 ml) was hydrogenated over 10% Pd/C (100 mg) at room

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temperature and atmospheric pressure for 2.5 hr. Removal of catalyst and solvent afforded **5** (0.262 g) in 85% yield, m.p. 149-50° (lit.[1] m.p. 148-50°).

(±)-*Combretastatin* (**1**)

To a solution of **5** (0.15 g) in ethanol (10 ml), $NaBH_4$ (25 mg) was added and stirred for 0.5 hr. Usual work-up and chromatographic purification afforded pure (±)-**1** (0.14 g, 90%) which crystallised from benzene in clolurless needles, m.p. 110-12° (lit.[2] m.p. 130-31°).

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Synthesis of 5α-Cyanocholestan-6-ones

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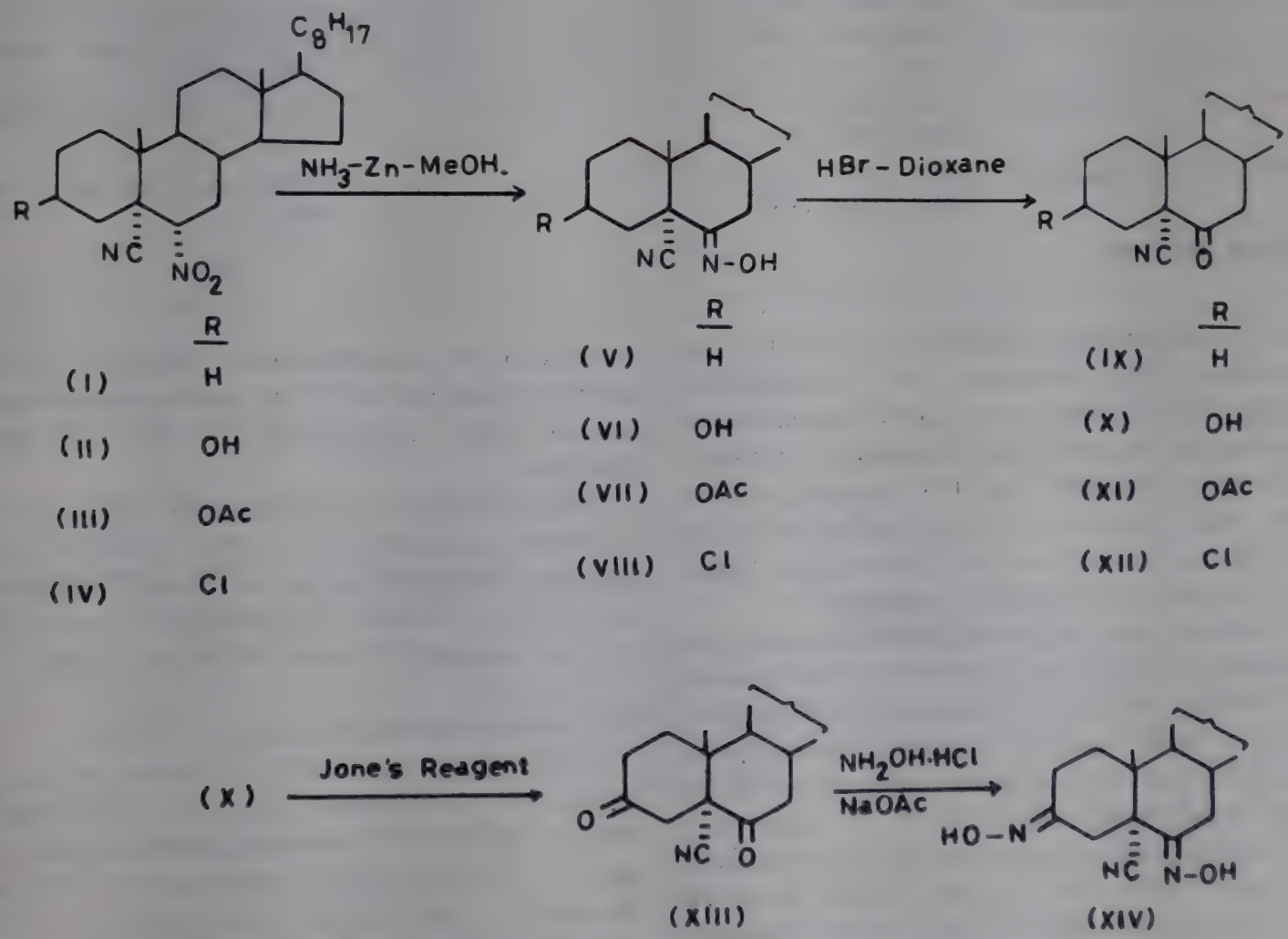
Synthesis of 5α-cyanocholestan-6-ones (IX-XII) from the respective oximes (V-VIII), obtained by the reaction of nitrocyanides (I-IV) with NH_3-Zn-MeOH, is described. From X, 5α-cyanocholestane-3,6-dione (XIII) and subsequently dioxime (XIV) have also been obtained. These cyanosteroids which are otherwise difficult to prepare form a series of new useful substrates.

In the recent past a number of papers[1-4] describing the synthesis of β-cyanoketones through the Michael condensation of steroidal α,β-unsaturated ketones with KCN have been published. But, the steroidal α-cyanoketones perhaps due to the lack of a clear-cut procedure for their synthesis could not be reported. In the present synthesis of 5α-cyanocholestan-6-ones, our earlier procedure[5] for the preparation of oximes from steroidal nitroolefins has been successfully employed and its validity demonstrated in oximating 5α-cyano-6-nitrocholestanes (I-IV)[6] with the reagent NH_3-Zn-MeOH. The oximes V-VIII thus obtained were hydrolysed to the respective 6-ones (IX-XII) in excellent yields by a selective solvent system consisting of hydrobromic acid and dioxane. Oxidation of X with Jone's reagent furnished XIII, which on treatment with $NH_2OH.HCl$/NaOAc produced the dioxime XIV (Scheme 1).

The products V-XIV were characterized on the basis of their elemental analyses and spectral data (IR and PMR) (Table 1). In particular, the oximes V-VIII showed in their IR spectra absorption bands at 3500-3400 (NOH) and 1650-1670 cm^{-1} (C=N) which are typical of oximes. Their PMR spectra displaying a doublet around δ 3.40 for one of the C-7 protons and a one-proton singlet in the region 8.5-9.8 assignable for the oxime OH proton, fully supported the structures assigned to them.

The notable feature in the IR spectra of the cyanooximes is the appearance of comparatively sharp bands (very sharp in the case of oxime VIII) shifted slightly to longer wavelengths (3500-3400 cm^{-1}) in



	R
(I)	H
(II)	OH
(III)	OAc
(IV)	Cl

	R
(V)	H
(VI)	OH
(VII)	OAc
(VIII)	Cl

	R
(IX)	H
(X)	OH
(XI)	OAc
(XII)	Cl

(X) → (XIII) → (XIV)

Scheme 1

Table 1—Characterization Data of the Products V-XIII

Compd	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	N	IR (cm^{-1})	PMR (δ, ppm)
V	70	178	$C_{28}H_{46}N_2O$	78.8 (78.9)	10.9 (10.8)	6.6 (6.6)	—	8.83 (*s*, 1H, N−OH*), 3.36 (*d*, J=11 Hz, 1H, C_7-H), 0.90 (*s*, 3H, C_{10}-CH_3), 0.63 (*s*, 3H, C_{13}-CH_3), 0.86 and 0.83 (other methyl protons)
VI	75	215	$C_{28}H_{46}N_2O_2$	76.1 (76.0)	10.5 (10.4)	6.4 (6.3)	—	9.80 (*s*, 1H, N−OH*), 4.20 (*m*, $W_{\frac{1}{2}}$=20 Hz, 1H, C_3-αH), 3.85 (broad *s*, 1H, C_3-OH*), 3.35 (d-like, J=10 Hz, 1H, C_7-H), 0.90 (*s*, 3H, C_{10}-CH_3), 0.67 (*s*, 3H, C_{13}-CH_3), 0.87 and 0.82 (other methyl protons)
VII	70	221	$C_{30}H_{48}N_2O_3$	74.5 (74.4)	10.0 (9.9)	5.9 (5.8)	—	8.50 (sharp *s*, 1H, N−OH*), 5.20 (*m*, $W_{\frac{1}{2}}$=20 Hz, 1H, C_3-αH), 3.35 (*d*, J=11 Hz, 1H, C_7-H), 2.05 (*s*, 3H, (C_3-$OCOCH_3$), 0.94 (*s*, 3H, C_{10}-CH_3), 0.67 (*s*, 3H, C_{13}-CH_3), 0.87 and 0.82 (other methyl protons)
VIII	72	182	$C_{28}H_{45}N_2OCl$	72.9 (73.0)	9.9 (9.8)	6.0 (6.1)	—	8.53 (sharp *s*, 1H, N−OH*), 4.30 (*m*, $W_{\frac{1}{2}}$=22 Hz, 1H, C_3-αH), 3.40 (*d*, J=10 Hz, 1H, C_7-H), 0.91 (*s*, 3H, C_{10}-CH_3), 0.67 (*s*, 3H, C_{13}-CH_3), 0.83 and 0.88 (other methyl protons)
IX	80	119	$C_{28}H_{45}NO$	81.7 (81.8)	11.0 (11.0)	3.4 (3.4)		2240 (C≡N), 1725 (C=O)
X	85	105	$C_{28}H_{45}NO_2$	78.8 (78.7)	10.5 (10.5)	3.2 (3.2)		3400 (broad, C_3-OH), 2230 (C≡N), 1725 (C=O)
XI	80	122	$C_{30}H_{47}NO_3$	76.8 (76.8)	10.1 (10.0)	3.1 (3.0)		2235 (C≡N), 1725 (C=O), 1730 ($OCOCH_3$) (merged together), 1230, 1050 (C−O)
XII	80	147	$C_{28}H_{44}NOCl$	75.5 (75.4)	9.9 (9.9)	3.2 (3.1)		2230 (C≡N), 1730 (C=O), 760 (C−Cl)
XIII	80	191	$C_{28}H_{43}NO_2$	79.1 (79.1)	10.2 (10.1)	3.3 (3.3)		2230 (C≡N), 1730 (3-CO), 1710 (6-CO)

*Exchangeable with D_2O.

contrast to the broad absorption bands for the corresponding OH stretching in 6-oximino-5α-cholestanes[5]. This phenomenon can be explained by considering the intramolecular hydrogen bonding[7,8] between the oxime OH and CN groups in these products. The hydrolysis of the cyanooximes to the ketones taking longer reaction period and higher temperature supports the above viewpoint.

A noteworthy point regarding the IR spectra of the cyanoketones is a 15-20 cm^{-1} increase in the frequency of C-6 carbonyl group in comparison to the normal frequency of this function in α-unsubstituted steroidal 6-ones. This is due to the presence of CN group α to the carbonyl group which shifts the νC=O band to a higher frequency as has been observed in the case of α-haloketones[9]. This effect is quite evident in the IR spectrum of the cyanodiketone XIII which exhibited a bifurcated band at 1710 and 1730 cm^{-1}. The latter band can be unambiguously assigned to the C-6 carbonyl function while the former appearing at the normal value corresponds to the C-3 carbonyl function.

Melting points are uncorrected. IR spectra were recorded in KBr on a P.U. SP3-100 infrared spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ on a Varian A 60 instrument using TMS as internal standard (chemical shifts in δ, ppm).

5α-Cyano-6-oximinocholestanes (V-VIII)

Zinc dust (6 g) was added to a stirred solution of 5α-cyano-6-nitrocholestane (2 g) in ether-methanol mixture (100 ml; 1:1) containing ammonia solution (sp. gr. 0.91; 40 ml) at room temperature (25-35°) and the progress of the reaction monitored by TLC. The reaction was over within 15-30 min. Thereafter, the suspension was filtered, the filtrate reduced on a

steam-bath, the residue mixed with a large amount of water and extracted with ether. The ethereal layer was washed with water, dried (anhyd. Na_2SO_4), and the solvent evaporated to get a solid which on crystallization from methanol provided the corresponding oxime in 70-75% yield as shining crystal (another product formed in minute quantity was not characterized).

5α-*Cyanocholestan*-6-*ones* (*IX-XII*)

A solution of the appropriate oxime (1 g) in dioxane (25 ml) and HBr (10 ml; 40%) was refluxed on a heating mantel for varying periods (8-40 hr) and the progress of the reaction monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (~2%) and water, dried (anhyd. Na_2SO_4), filtered and the solvent evaporated on a steam bath. Crystallization of the residue from methanol-ether provided the corresponding cyanoketone in 80-85% yield.

5α-*Cyanocholestane*-3,6-*dione* (*XIII*)

To a stirred solution of X (1 g) in acetone (30 ml) and cooled to 0-5°, was added Jone's reagent (10 ml) dropwise during 20 min. The stirring was continued further for half an hour. The reaction mixture was then mixed with water, worked-up in the usual way with ether. Removal of the solvent gave a solid which was crystallized from methanol to give XIII, yield 0.8 g m.p. 191°.

5α-*Cyano*-3,6-*dioximinocholestane* (*XIV*)

A mixture of XIII (0.5 g) in methanol (30 ml), hydroxylamine hydrochloride (1.5 g) and sodium acetate (1 g) was warmed on a steam-bath for 20 min, poured into water and extracted with chloroform. The organic layer was washed with water, dried (anhyd. Na_2SO_4) and filtered. Evaporation of the solvent and crystallization of the residue from methanol gave the cyanodioxime XIV, yield 0.49, m.p. 245°, IR: 3620-3180 (broad, NOH), 2230 (C = N), 1660 (C ≡ N (Found C, 73.8; H, 10.0; N; 9.2. $C_{28}H_{45}N_3O_2$ requires C, 73.9; H, 9.9; N, 9.2%).

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Synthesis of Rubraflavone-ATrimethyl Ether

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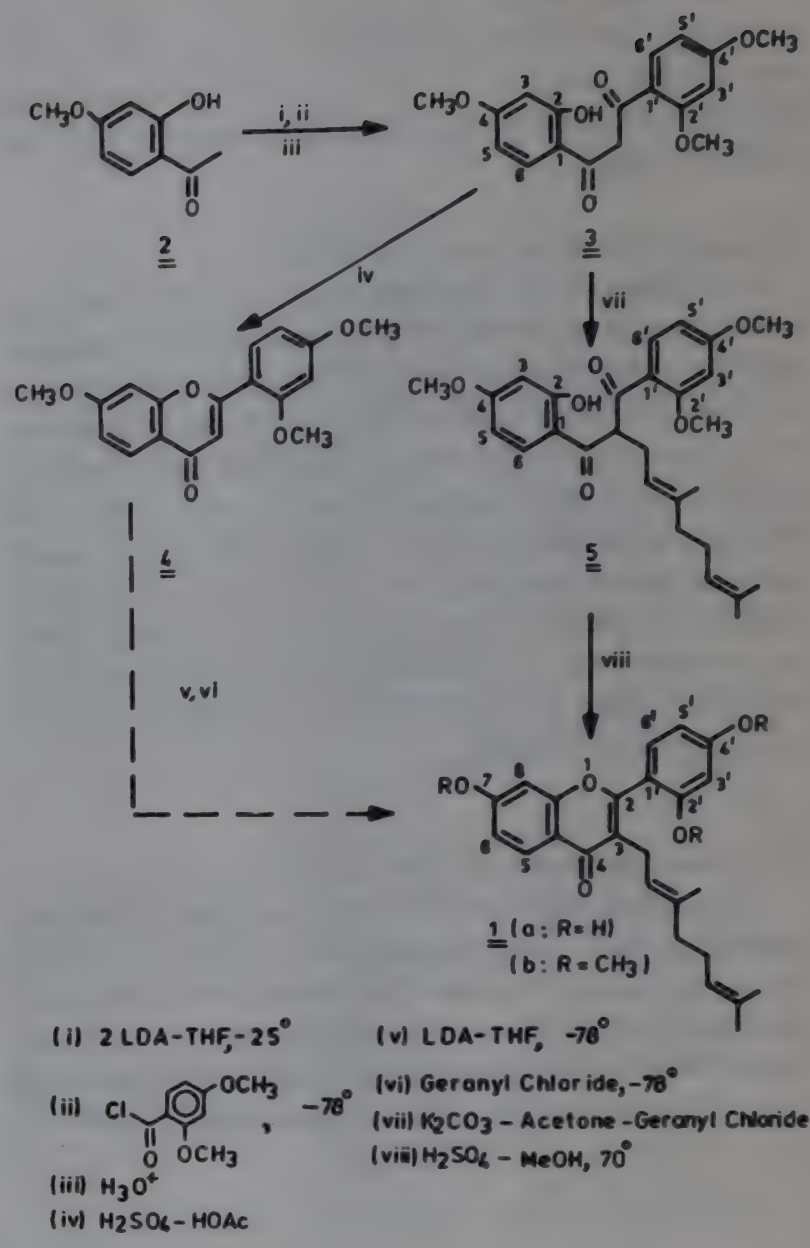
The synthesis of rubraflavone-A trimethyl ether (**1b**) involves aroylation of lithium enolate of 2-hydroxy-4-methoxyacetophenone (**2**) with 2,4-dimethoxybenzoyl chloride to yield β-diketone (**3**) which is alkylated with geranyl chloride in the presence of K_2CO_3 to obtain the 1,3-dioxo compound (**5**). Cyclisation of **5** to rubraflavone-A trimethyl ether (**1b**) is easily accomplished using acid catalyst.

Rubraflavone-A, isolated[1] from the bark of *Morus rubra* Linn. and the first naturally occurring flavone containing C_{10}-terpenoid chain at C-3, was assigned structure (**1a**) on the basis of spectroscopic analyses[1]. However, the synthesis of this compound is yet to be reported. This note presents the synthesis of rubraflavone-A trimethyl ether (**1b**).

Two possible routes were attempted. However, our first attempt, which involved regiospecific deprotonation of appropriately substituted flavone (**4**) at C-3 with lithium diisopropylamide[2] followed by alkylation of the anion with geranyl chloride did not succeed. The failure to get **1b** may be due to its decomposition[3] in strongly basic conditions (presence of anion of **4** and lithium diisopropylamide). **1b** is a 'skipped methylene compound' and such compounds are known to be unstable under strongly basic conditions[3].



In the alternate route, alkylation of appropriately substituted β-diketone (**3**) with geranyl chloride in the presence of milder base (K_2CO_3) was envisaged. The required β-diketone (**3**) was prepared in good yield through aroylation of lithium enolate of 2-hydroxy-4-methoxyacetophenone (**2**) with 2,4-dimethoxybenzoyl chloride[4]. Alkylation of **3** with geranyl chloride in the presence of K_2CO_3 afforded 2-geranyl-1,3-dioxo compound (**5**). The structure of **5** was consistent with the spectral data (see its preparation below). Cyclodehydration of **5** to rubraflavone-A trimethyl ether (**1b**) was conveniently effected using catalytic amount of H_2SO_4 in methanol. The spectral data of flavone (**1b**) were in agreement with the assigned structure and its physical properties were identical with those reported in literature[1].

Melting points are uncorrected. UV spectra were recorded in spectral grade methanol on a Ziess RQ 20 PA recording spectrophotometer, IR spectra (KBr) on a Perkin-Elmer 237 spectrophotometer and PMR spectra in $CDCl_3$ on a Varian A-60 A spectrometer using TMS as an internal standard. TLC was carried out using silica gel.

1,3-*Dioxo*-1-(2-*hydroxy*-4-*methoxyphenyl*)-3-(2,4-*dimethoxyphenyl*)*propane* (**3**)

It was prepared from 2-hydroxy-4-methoxyacetophenone (**2**) and 2,4-dimethoxybenzoyl chloride following our earlier method[4], and recrystallised from ether, m.p. 125°, yield 67%; UV: 395, 380 and 308 nm (log ε 4.08, 4.13 and 3.95); IR: 1625, 1565, 1510 and 1410 cm^{-1}; PMR: δ 3.66, 3.83 and 3.97 (*s*, each, 9H, 3 × OCH_3) 4.47 (*s*, 1.1H, $-COCH_2CO-$, keto form, 54%), 6.43-6.65 (*m*, 4H, 3-H, 5-H, 3'-H and 5'-H), 7.15 (*s*, 0.9H, $-COCH=C(OH)-$, enol tautomer 46%), 7.62 (*d*, 1H, 6'-H, J = 10Hz), 8.0 (*d*, 1H, 6-H, J = 10Hz), 12.57 (*s*, −OH, chelated hydroxyl, keto form), 12.77 (*s*, −OH, chelated hydroxyl, enol form), 15-72 (*s*, −OH, enolic hydroxyl); MS: *m/z* 330 (M^+) (Found: C, 65.4; H, 5.5. $C_{18}H_{18}O_6$ requires C, 65.5; H, 5.5%).

1,3-*Dioxo*-1-(2-*hydroxy*-4-*methoxyphenyl*)-2-*geranyl*-3-(2,4-*dimethoxyphenyl*)*propane* (**5**)

To a solution of **3** (950 mg, 2.88 mmol) in dry acetone (30 ml) was added anhyd potassium carbonate (2 g). To this mixture, geranyl chloride (600 mg, 3.49 mmol) was added, contents were refluxed with stirring for 24 hr, cooled and filtered. Removal of solvent from the filtrate followed by preparative layer chromatography of the crude product (benzene-ethyl acetate, 9:1, multiple development) resulted in pure **5** (287 mg) as deep yellow oil; UV: 310 and 272 nm (log ε 4.12 and 4.24); IR: 3500, 2950, 1680, 1640, 1610 cm^{-1}; PMR: δ 1.60 (*br*, 9H, $3\times -C=C-CH_3$), 1.97 (*m*, 6H, $3\times -C=C-CH_2-$), 3.53 (*s*, 3H, $-OCH_3$), 3.80 (*s*, 6H, $2\times OCH_3$); 5.15 (*t*, 3H, $2\times -C=CH-CH_2-$ and $-COCHCO-$), 6.25-6.53 (*m*, 4H, 3-H, 5-H, 3′-H, 5′-H), 7.63 (*d*, H, 6′-H, $J=10$Hz), 7.83 (*d*, H, 6-H, $J=10$Hz), 12.53 (2*s*, H, −OH, chelated hydroxyl group of keto- and enol tautomers); MS: (*m/z* 466 M^+). The compound (**5**) was used as such for the next stage.

Rubraflavone-A trimethyl ether (**1b**)

To a solution of **5** (50 mg) in methanol (3 ml) was added conc sulphuric acid (1 drop) and refluxed (oil-bath at 70°), the progress of the reaction being monitored by TLC (benzene). After 1 hr methanol was evaporated and the residue purified by preparative layer chromatography (benzene) to obtain pure **1b** (36 mg), which was recrystallised from ether-hexane, m.p. 80-81° (lit. m.p. 79°); UV: 300 and 248 nm (log ε 4.12 and 4.22); IR: 2990, 1640, 1600, 1525 and 1460 cm^{-1}; PMR: δ 1.40 (*s*, 3H, $-C=C-CH_3$), 1.55 (*s*, 3H, $-C=C-CH_3$), 1.62 (*s*, 3H, $-C=C-CH_3$) 1.90 (*bs*, 4H, $2\times -C=C-CH_2-$); 3.05 (*d*, 2H, $-C=C-CH_2-CH=C-$, doubly allylic), 3.77 (*s*, 3H, $-OCH_3$), 3.82 (*s*, 6H, $2\times -OCH_3$), 5.07 (*bs*, 2H, $-C=CH-CH_2-$), 6.40 to 6.60 (*m*, 2H, 6-H and 8-H) 6.67-7.0 (*m*, 2H, 3′-H and 5′-H), 7.17 (*d*, 1H, 6′-H, $J=8$Hz), 8.07 (*d*, 1H, 5-H, $J=9$Hz); MS: *m/z* 448 (M^+) (Found: C, 74.72; H, 7.38. $C_{28}H_{32}O_5$ requires C, 75.00; H, 7.14%).

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Synthesis & Reactions of 4α-Acetoxycar-2-ene†

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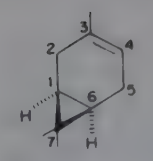
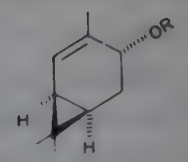
Epoxidation of 4α-acetoxycar-2-ene (III) with perbenzoic acid gives in addition to the epoxide IV, the rearranged hydroxy acetate (V). Under acidic conditions in different solvents, the epoxide IV rearranges to *p*-menthane derivatives V, VII and VIII. Rearrangement of IV under basic conditions gives rise to the *p*-menthane derivative IX which on oxidation with Jones chromic acid reagent gives as one of the products, a conjugated keto-γ-lactone, identified as X by spectral data.

In previous communications[1,2] from this laboratory, epoxidation studies on 4α-substituted car-2-ene derivatives, possessing different substituents have been described. With a view to ascertaining the effect of substituent at C-4 on the cleavage of the epoxide ring, the epoxide IV has now been prepared from 4α-acetoxycar-2-ene (III) and the results of its rearrangements under acidic and basic conditions are reported in this note.

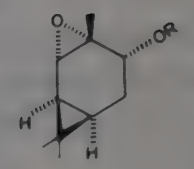


I



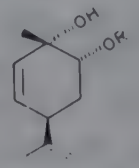
II, R = H

III, R = $-\overset{O}{\overset{\|}{C}}-CH_3$

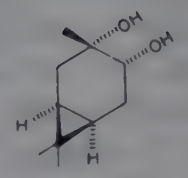


IV, R = $-\overset{O}{\overset{\|}{C}}-CH_3$

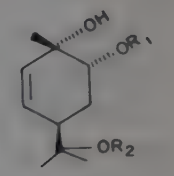
XI, R = H



V, R = $-\overset{O}{\overset{\|}{C}}-CH_3$

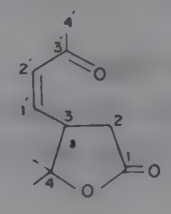


VI



VII, R_1 = $-\overset{O}{\overset{\|}{C}}-CH_3$, $R_2 = CH_3$

VIII, R_1 = $-\overset{O}{\overset{\|}{C}}-CH_3$, R_2 = H



X

IX, R_1 = H, R_2 = H

In previous communications[1,2] from this laboratory, epoxidation studies on 4α-substituted car-2-ene derivatives, possessing different substituents have been described. With a view to ascertaining the effect of substituent at C-4 on the cleavage of the epoxide ring, the epoxide IV has now been prepared from 4α-acetoxycar-2-ene (III) and the results of its rearrangements under acidic and basic conditions are reported in this note.

4α-Acetoxycar-2-ene (III) was prepared by acetylation (Ac_2O/Py) of 4α-hydroxycar-2-ene (II), which in turn was obtained as one of the products of the base-catalysed rearrangement of carane-3α,4α-epoxide, by the method developed in our laboratory (unpublished work).

Treatment of III with perbenzoic acid gives mainly two compounds (TLC, 2 spots; 8% ethyl acetate in benzene) which were separated by chromatography over silicic acid. The less polar compound, the major product obtained as a liquid, was identified as the epoxide IV by elemental analysis and spectral data $-C_{12}H_{18}O_3$, M^+ 210, $[\alpha]_D^{28}+83.8°$ (*c*, 2.5; $CHCl_3$); IR‡: 1730, 1242 (acetate), 1024 (1,2-epoxide); PMR‡(CCl_4): 0.8 (2H, *m*, C_1-H and C_6-H), 1.11, 1.18 (3H each, *s* each, C_7-*gem*-dimethyl protons), 1.25 (2H, *s*, $C-CH_3$), 1.93 (2H, *m*, 5-CH_2), 2.1 (3H, *s*, $-OCOCH_3$), 3.05 (1H, br *s*, C_2-H) and 5.11 (1H, *t*, J = 7 Hz, C_4-H).

The more polar compound obtained as a liquid (TLC-pure), was identified as V ($C_{12}H_{18}O_3$; M^+ 210) by spectral data; IR: 3448 (OH), 1730, 1242 (acetate), 1642 ($>C=CH_2$); PMR(CCl_4): 1.15 (3H, *s*, C_1-CH_3), 1.6 (3H, *s*, vinylic methyl at C-8), 1.88 (5H, *s*, overlapping a multiplet, $-OCOCH_3$ and 3-CH_2), 2.58 (1H, *m*, allylic C_4-H), 4.31-4.43 (3H, *s*, overlapping a multiplet, $>C=CH_2$ and proton at C_2-H) and 5.06 (2H, *s*, olefinic protons at C-5 and C-6).

LAH reduction of IV afforded a crystalline diol, $C_{10}H_{18}O_2$, M^+ 170, m.p. 68° (pet. ether), $[\alpha]_D^{28}+14.5°$ (*c*, 1.2; $CHCl_3$) which was identified as *cis*-3α,4α-caranediol (VI) by comparing the spectral data with those reported in literature[2]; IR: 3448 (OH); PMR(CCl_4): 0.66 (2H, *m*, C_1-H and C_6-H), 0.88, 0.98 (3H each, *s* each C_7-*gem*-dimethyl protons), 1.12 (3H, *s*, C_3-CH_3), 1.81 (4H, *m*, 2-CH_2 and 5-CH_2), 2.96 (1H, *q*, C_4-H) and 3.5 (2H br *s*, exchangeable with D_2O, 2×OH). Formation of VI from IV establishes the stereochemistry of the epoxide at C_2-C_3 as α, as shown in the stereostructure IV. It is thus confirmed that the approach of the reagent is from the less hindered α-side. The approach from β-side is restricted because of the β-oriented cyclopropane ring with *gem*-dimethyl group.

The epoxide IV underwent rearrangement in acidic conditions [catalytic quantity of hydrochloric acid[3], (1*N*) in methanol at 0°] to give a mixture of two compounds (TLC, 2 spots; 8% ethyl acetate in benzene). The mixture was resolved by column chromatography over silicic acid. The less polar

†NCL Communication No. 3800

‡IR ν_{max} in cm^{-1} and PMR chemical shifts (downfield from TMS) in δ, ppm throughout the article.

constituent was the minor product, obtained as a liquid and was identified as V by co-TLC and spectral data. The more polar compound, obtained as a liquid ($C_{13}H_{22}O_4$, M^+ 242), was identified as VII on the basis of spectral data; IR: 3448 (OH), 1730, 1242 (acetate), 1640, 740 (*cis*-disubstituted double bond); PMR(CCl_4): 1.1 (6H, *s*, C_8-*gem*-dimethyl protons), 1.26 (3H, *s*, C_1-CH_3), 1.56 (2H, *m*, 3-CH_2), 1.75 (1H, *hump*, exchangeable with D_2O, $-OH$), 2.08 (4H, *s*, overlapping a multiplet, $C_2-OCOCH_3$ and C_4-H), 3.18 (3H, *s*, $-OCH_3$), 4.86 (1H, br *m*, C_2-H) and 5.65 (2H, br *s*, olefinic protons).

When the epoxide IV was treated with a catalytic quantity of HCl in dioxan-water, a mixture of two products (TLC, 2 spots; 15% ethyl acetate in benzene) was obtained. It was resolved by column chromatography. The less polar compound (the minor product) was obtained as a liquid and identified as V, by co-TLC and IR and PMR data.

The more polar compound, obtained as a solid, was identified as the dihydroxy acetate VIII, $C_{12}H_{20}O_4$, M^+ 228, m.p. 99°; IR: 3448 (OH), 1724, 1248 (acetate), 740 ($>C=CH$); PMR(CCl_4): 1.13, 1.18 (3H each, *s* each, C_8-*gem*-dimethyl protons), 1.23 (3H, *s*, C_1-CH_3), 1.81, 1.95 (4H, *m*, partly exchangeable with D_2O, 2 × OH and 3-CH_2), 2.03 (3H, *s*, $C_2-OCOCH_3$), 2.18 (1H, *m*, C_4-H), 4.78 (1H, br *m*, C_2-H) and 5.55 (2H, br *s*, olefinic protons).

The epoxide IV on treatment with a strong alkali like KOH in DMSO, gave a crude liquid product, which after purification by chromatography gave a solid. It was crystallized from ethyl acetate and identified as the triol IX, $C_{10}H_{18}O_3$, M^+ 186, m.p. 76°; IR: 3333 (OH); PMR(CCl_4): 1.2, 1.24 (3H each, *s* each, C_8-*gem*-dimethyl protons), 1.3 (3H, *s*, C_1-CH_3), 1.94 (5H, *s*, overlapping a multiplet, partly exchangeable with D_2O, 3 × OH and 3-CH_2), 2.32 (1H, *m*, C_4-H), 3.86 (1H, br *m*, C_2-H) and 5.78 (2H, *dd*, $J_1 = 6.4$ Hz, $J_2 = 11.2$ Hz, olefinic protons).

The structure of triol IX was further confirmed by the following reactions: (a) Oxidation of IX with Jones chromic acid reagent, gave a conjugated keto-γ-lactone ($C_{10}H_{14}O_3$, M^+ 182) as a liquid from the neutral part. It was identified as X by spectral data; IR: 1780 (γ-lactone), 1680 (Conju. $>C=O$), 1620 (Conju. $>C=C<$); PMR(CCl_4): 1.26, 1.52 (3H each, *s* each, C_4-*gem*-dimethyl protons), 2.32 (3H, *s*, $-COCH_3$), 2.73 (2H, *d*, $J = 8$ Hz, 2-CH_2), 3.02 (1H, *m*, C_3-H), 6.24 (1H, *d*, $J = 14.4$ Hz, olefinic proton at C-2′) and 6.74 (1H, *dd*, $J_1 = 8$ Hz, $J_2 = 14.4$ Hz, olefinic proton at C-1′). The formation of X from IX proved the presence of a vicinal diol grouping in IX. (b) The triol IX on acetylation with Ac_2O/Py afforded a solid product, identical (m.p., m.m.p., co-TLC, IR, PMR) with VIII (the secondary hydroxyl group of IX gets acetylated while tertiary hydroxyl group remains unaffected).

However, when IV was treated with methanolic KOH, it underwent hydrolysis without cleavage or rearrangement reaction to give a liquid product which was identified as the epoxyalcohol XI, $C_{10}H_{16}O_2$, M^+ 168; IR: 3448 (OH), 1024 (epoxide); PMR(CCl_4): 0.75 (2H, *m*, C_1-H and C_6-H), 0.98, 1.11 (3H each, *s* each, C_7-*gem*-dimethyl protons), 1.35 (3H, *s*, C_3-CH_3), 1.56, 1.9 (2H, *m*, 5-CH_2), 2.28 (1H, *hump*, exchangeable with D_2O, $-OH$), 3.1 (1H, *s*, C_2-H) and 3.93 (1H, *m*, C_4-H).

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Acid Azides: Part X†—New Synthesis & Decomposition Reactions of Phthalimidobenzoic Acid Azides‡

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The *o*-, *m*-, and *p*-phthalimidobenzoic acid azides (IIa-c) have been synthesized via the reaction of the corresponding acid chlorides (Ia-c) with aq. NaN_3 in acetone. The base-catalyzed decomposition of IIa-c with aromatic amines and/or hydrazines shows that *o*- and *p*-substituted azides (IIa and IIc) react via the azido group displacement to give the corresponding anilides (IIIa-n) and/or hydrazides (IVa-f). However, *m*-substituted azide (IIb) reacts via Curtius rearrangement to give the corresponding urea derivatives (Va-g). Acid-catalyzed decomposition of the azides IIa and IIc with anhyd. $AlCl_3$ in aromatic substrates give the corresponding ketones (IX) via the azido group displacement. However, the *m*-substituted azide IIb gives the anilide derivative (Xb) via Curtius rearrangement.

In the present investigation, we have introduced the phthalimido moiety into the *o*-, *m*-, and *p*-positions of benzoic acid molecule with the object of studying the behaviour of the resulting acid azides towards acid- and base-catalyzed decomposition. The title azides (II) were prepared by reacting *o*-, *m*-, and *p*-phthalimidobenzoic acid chlorides (Ia-c) with aq. NaN_3 in acetone.

The base-catalyzed decomposition of the azides IIa and IIb with aromatic amines and aminobenzoic acids, namely aniline, *p*-toluidine, *p*-anisidine, *p*-chloroaniline and *o*-, *m*- and *p*-aminobenzoic acids afforded the corresponding anilides (IIIa-n) (Scheme 1).

Similarly, the acid azides IIa-c underwent base-catalyzed decomposition with hydrazine hydrate and phenylhydrazine yielding the corresponding phthalimidobenzoic acid hydrazides (IVa-f).

The structures of IIIa-n and IVa-f were established by direct comparison (m.m.p.) with authentic specimens prepared by the reaction of the corresponding acid chlorides (Ia-c) with the above mentioned aromatic amines, aminobenzoic acids and/or hydrazines. This showed that the reaction took place via the azido group displacement in the case of *o*- and *p*-phthalimidobenzoic acid azides. However, *m*-phthalimidobenzoic acid azide (IIc) reacted with the same aromatic amines and aminobenzoic acids under similar reaction conditions to give N-(aryl or carboxyphenyl)-N′-(3′-phthalimidophenyl)ureas (Va-g).

The structure of V was established unambiguously by the reaction of *m*-phthalimidophenyl isocyanate (VIb) with the above mentioned aromatic amines and aminobenzoic acids under similar reaction conditions to give V. Compound IIb reacted with aromatic amines via Curtius rearrangement to give the corresponding urea derivatives (Va-g). This behaviour is similar to that stated earlier for benzoic acid azides[6].

It was also found that *o*- and *p*-phthalimidophenyl isocyanates (VIa and VIc) reacted with the above aromatic amines and aminobenzoic acids under similar conditions to give the corresponding urea derivatives (Vh-n) and Vo-(Vo-u).

The isocyanates VIa-c reacted with hydrazine hydrate and phenylhydrazine to give N-phthalimidophenylsemicarbazides (VIIa-f), but underwent hydrolysis with water to give *sym*-N,N′-di(phthalimidophenyl)ureas (VIIIa-c).

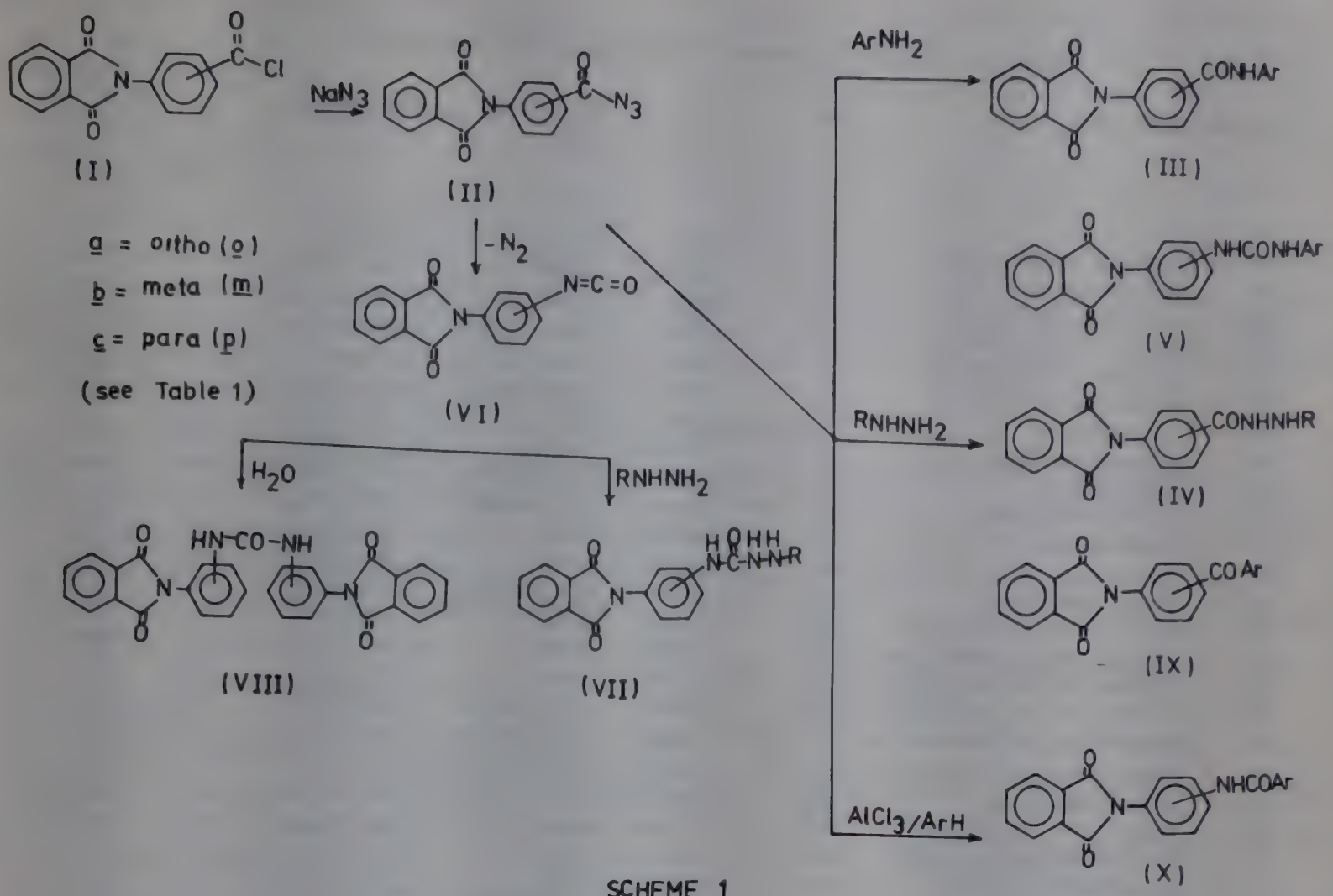
Lewis acid-catalyzed decomposition of *o*- and *p*-phthalimidobenzoic acid azides (IIa and IIc) by anhyd. $AlCl_3$ in the presence of aromatic substrates such as benzene, toluene and anisole was found to give the corresponding N-(2- or 4-aroylphenyl)phthalimides (IXa and IXc), the structures of which were established by direct comparison (m.m.p.) with authentic specimens prepared by the reaction of the corresponding acid chlorides (Ia and Ic) with the same aromatic substrates in the presence of anhyd. $AlCl_3$.

However, *m*-phthalimidobenzoic acid azide (IIb) reacted with benzene, toluene and anisole in the presence of anhyd. $AlCl_3$ under similar conditions by a different route to give the corresponding *m*-pthalimidobenzoic acid anilides (Xb_{1-3}). The structure of Xb was established authentically via the reaction of VIb with the above mentioned aromatic substrates in the presence of anhyd. $AlCl_3$ under similar reaction conditions.

Compounds Xa_{1-3} and Xc_{1-3} could also be synthesized by the reaction of the isocyanates VIa and VIc with benzene, toluene and anisole in the presence of anhyd. $AlCl_3$.

All melting points reported are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer (ν_{max} in cm^{-1}). The characteri-

†For Parts I-IX of the series, see references 1-9 respectively.
‡Presented in the twelvth (XII) Egyptian Chemical Conference, Cairo, 7-10 April 1984.



SCHEME 1

zation data of all the synthesized compounds are given in Table 1.

Phthalimidobenzoic acid azides (*IIa-c*; *Table* 1)

A solution of NaN_3 (0.15 mol) in the least amount of water was added dropwise into a cold solution of I (0.1 mol) (ice-bath) in dry acetone (50 ml) under stirring. The stirring was continued for half an hour and the reaction mixture poured onto iced-water. The resulting solid was recrystallized from dry ether to give II; IR: 2240-2200 (N_3), 1700-1680 (acid azide C=O), 1780-1760 and 1720-1710 (C=O coupling bands of cyclic imides)[10,11].

Action of aromatic amines, aminobenzoic acids and/or hydrazines on acid azides (*IIa-c*) *and phenyl isocyanates*

Table 1—Characterization Data of the Synthesized Compounds

Compd	Side chain	Yield (%)	m.p. °C	Crystallized from	Mol. formula	N(%)*	
						Found	Calc.
Ia	COCl (*o*)	65	208-10	C_6H_6	$C_{15}H_8NO_3Cl$	4.9	4.9
Ib	COCl (*m*)	70	2 216-18	C_6H_6	$C_{15}H_8NO_3Cl$	5.0	4.9
Ic	COCl (*p*)	67	272-74	C_6H_6	$C_{15}H_8NO_3Cl$	5.0	4.9
IIa	CON_3 (*o*)	60	102-4	Ether	$C_{15}H_8N_4O_3$	19.2	19.2
IIb	CON_3 (*m*)	60	138-40	Ether	$C_{15}H_8N_4O_3$	19.3	19.2
IIc	CON_3 (*p*)	50	212-14	Ether	$C_{15}H_8N_4O_3$	19.2	19.2
IIIa	$(CONHC_6H_5)o$-	68	206-8	C_6H_6-MeOH	$C_{21}H_{14}N_2O_3$	8.2	8.2
IIIb	$[CONHC_6H_4CH_3(p\text{-})]o$-	65	210-12	C_6H_6-MeOH	$C_{22}H_{16}N_2O_3$	7.9	7.9
IIIc	$[CONHC_6H_4OCH_3(p\text{-})]o$-	62	168-70	C_6H_6-MeOH	$C_{22}H_{16}N_2O_4$	7.6	7.5
IIId	$[CONHC_6H_4Cl(p\text{-})]o$-	70	148-50	C_6H_6	$C_{21}H_{13}N_2O_3Cl$	7.5	7.4
IIIe	$[CONHC_6H_4COOH(o\text{-})]o$-	60	184-86	C_6H_6-MeOH	$C_{22}H_{14}N_2O_5$	7.2	7.3
IIIf	$[CONHC_6H_4COOH(m\text{-})]o$-	62	128-30	C_6H_6-MeOH	$C_{22}H_{14}N_2O_5$	7.2	7.3
IIIg	$[CONHC_6H_4COOH(p\text{-})]o$-	60	208-10	C_6H_6	$C_{22}H_{14}N_2O_5$	7.3	7.3
IIIh	$(CONHC_6H_5)p$-	55	>300	C_6H_6	$C_{21}H_{14}N_2O_3$	8.1	8.2

(*Contd*)

Table 1—Characterization Data of the Synthesized Compounds—*Contd*

Compd	Side chain	Yield (%)	m.p. °C	Crystallized from	Mol. formula	N(%)*	
						Found	Calc.
IIIi	$[CONHC_6H_4CH_3(p\text{-})]p$-	55	>300	EtOAc	$C_{22}H_{16}N_2O_3$	7.9	7.9
IIIj	$[CONHC_6H_4OCH_3(p\text{-})]p$-	62	256-58	EtOH	$C_{22}H_{16}N_2O_4$	7.6	7.5
IIIk	$-CONHC_6H4Cl(p\text{-})]p$-	60	>300	EtOH	$C_{21}H_{13}N_2O_3Cl$	7.5	7.4
IIIl	$[CONHC_6H_4COOH(o)]p$-	58	278-80	C_6H_6	$C_{22}H_{14}N_2O_5$	7.2	7.3
IIIm	$[CONHC_6H_4COOH(m)]p$-	58	260-62	C_6H_6	$C_{22}H_{14}N_2O_5$	7.2	7.3
IIIn	$[CONHC_6H_4COOH(p)]p$-	60	230-32	C_6H_6-MeOH	$C_{22}H_{14}N_2O_5$	7.2	7.3
IVa	$(CONHNH_2)o$-	55	>300	EtOH	$C_{15}H_{11}N_3O_3$	14.8	14.9
IVb	$(CONHNHC_6H_5)o$-	47	192-200	AcOH	$C_{21}H_{15}N_3O_3$	11.7	11.8
IVc	$(CONHNH_2)m$-	50	>300	C_6H_6-MeOH	$C_{15}H_{11}N_3O_3$	14.9	14.9
IVd	$(CONHNHC_6H_5)m$-	50	216-18	C_6H_6-MeOH	$C_{21}H_{15}N_3O_3$	11.7	11.8
IVe	$(CONHNH_2)p$-	55	284-86	EtOH	$C_{15}H_{11}N_3O_3$	14.8	14.9
IVf	$(CONHNHC_6H_5)p$-	52	240-42	EtOH	$C_{21}H_{15}N_3O_3$	11.8	11.8
Va	$(NHCONHC_6H_5)m$-	60	238-40	C_6H_6-MeOH	$C_{21}H_{15}N_3O_3$	11.9	11.8
Vb	$[NHCONHC_6H_4CH_3(p)]m$-	60	222-24	MeOH	$C_{22}H_{17}N_3O_3$	11.4	11.3
Vc	$[NHCONHC_6H_4OCH_3(p)]m$-	61	248-50	AcOH	$C_{22}H_{17}N_3O_4$	10.9	10.9
Vd	$[CONHCONHC_6H_4Cl(p)]m$-	68	242-44	AcOH	$C_{21}H_{14}N_3Cl$	10.8	10.7
Ve	$[NHCONHC_6H_4COOH(o)]m$-	52	148-50	C_6H_6-MeOH	$C_{22}H_{15}N_3O_5$	10.7	10.7
Vf	$[NHCONHC_6H_4COOH(m)]m$-	55	244-46	C_6H_6-MeOH	$C_{22}H_{15}N_3O_5$	10.6	10.7
Vg	$[NHCONHC_6H_4COOH(p)]m$-	50	268-70	C_6H_6-MeOH	$C_{22}H_{15}N_3O_5$	10.5	10.7
Vh	$(NHCONHC_6H_5)o$-	60	268-70	AcOH	$C_{21}H_{15}N_3O_3$	11.8	11.8
Vi	$[NHCONHC_6H_4CH_3(p)]o$-	60	154-56	C_6H_6	$C_{22}H_{17}N_3O_3$	11.3	11.3
Vj	$[NHCONHC_6H_4OCH_3(p)]o$-	68	228-30	EtOAc	$C_{22}H_{17}N_3O_4$	10.9	10.9
Vk	$[NHCONHC_6H_4Cl(p)]o$-	62	174-76	C_6H_6	$C_{21}H_{14}N_3O_3Cl$	10.8	10.7
Vl	$[NHCONHC_6H_4COOH(o)]o$-	58	146-48	C_6H_6-MeOH	$C_{22}H_{15}N_3O_5$	10.6	10.7
Vm	$[NHCONHC_6H_4COOH(m)]o$-	60	220-22	AcOH	$C_{22}H_{15}N_3O_5$	10.8	10.7
Vn	$[NHCONHC_6H_4COOH(p)]o$-	62	174-76	C_6H_6	$C_{22}H_{15}N_3O_5$	10.6	10.7
Vo	$(NHCONHC_6H_45)p$-	68	>300	AcOH	$C_{21}H_{15}N_3O_3$	11.8	11.8
Vp	$[NHCONHC_6H_4CH_3(p)]p$-	65	>300	AcOH	$C_{22}H_{17}N_3O_3$	11.2	11.3
Vq	$[NHCONHC_6H_4OCH_3(p)]p$-	70	>300	AcOH	$C_{22}H_{17}N_3O_4$	10.9	10.9
Vr	$[NHCONHC_6H_4Cl(p)]p$-	52	286-88	AcOH	$C_{21}H_{14}N_3O_3Cl$	10.8	10.7
Vs	$[NHCONHC_6H_4COOH(o)]p$-	62	254-56	C_6H_6-MeOH	$C_{22}H_{15}N_3O_5$	10.6	10.7
Vt	$[NHCONHC_6H_4COOH(m)]p$-	58	>300	AcOH	$C_{22}H_{15}N_3O_5$	10.7	10.7
Vu	$[NHCONHC_6H_4COOH(p)]p$-	60	>300	C_6H_6-MeOH	$C_{22}H_{15}N_3O_5$	10.7	10.7
VIIa	$(NHCONHNH_2)o$-	60	273-75	MeOH	$C_{15}H_{12}N_4O_3$	19.1	18.9
VIIb	$(NCONHNHC_6H_5)o$-	55	146-48	C_6H_6	$C_{21}H_{16}N_4O_3$	15.3	15.1
VIIc	$(NHCONHNH_2)m$-	58	290-92	MeOH	$C_{15}H_{12}N_4O_3$	18.9	18.9
VIId	$(NHCONHNHC_6H_5)m$-	60	>300 (-	C_6H_6-MeOH	$C_{21}H_{16}N_4O_3$	15.1	15.1
VIIe	$(NHCONHNH_2)p$-	62	270-72	MeOH	$C_{15}H_{12}N_4O_3$	18.9	18.9
VIIf	$(NHCONHNHC_6H_5)p$-	60	168-70	C_6H_6-MeOH	$C_{21}H_{16}N_4O_3$	15.1	15.1
VIIIa	NHCONH(2,2′)	60	222-24	C_6H_6	$C_{29}H_{18}N_4O_5$	11.7	11.6
VIIIb	NHCONH(3,3′)	58	>300	C_6H_6	$C_{29}H_{18}N_4O_5$	11.6	11.6
VIIIc	NHCONH(4,4′)	64	208-10	C_6H_6	$C_{29}H_{18}N_4O_5$	11.6	11.6
IXa_1	$(COC_6H_5)o$-	60	262-64	C_6H_6	$C_{21}H_{13}NO_3$	4.3	4.3
IXa_2	$[COC_6H_4CH_3(p)]o$-	64	254-56	C_6H_6	$C_{22}H_{15}NO_3$	4.0	4.1
IXa_3	$[COC_6H_4OCH_3(p)]o$-	68	206-8	C_6H_6	$C_{22}H_{15}NO_4$	3.8	3.9
IXc_1	$(COC_6H_5)p$-	67	179-81	C_6H_6	$C_{21}H_{13}NO_3$	4.3	4.3
IXc_2	$[COC_6H_4CH_3(p)]p$-	58	162-64	C_6H_6	$C_{22}H_{15}NO_3$	4.2	4.1
IXc_3	$[COC_6H_4OCH_3(p)]p$-	65	174-76	C_6H_6	$C_{22}H_{15}NO_4$	3.9	3.9
Xa_1	$(NHCOC_6H_5)o$	60	220-22	C_6H_6	$C_{21}H_{14}N_2O_3$	8.1	8.2
Xa_2	$[NHCOC_6H_4CH_3(p)]o$-	62	216-18	C_6H_6	$C_{22}H_{16}N_2O_3$	7.7	7.9
Xa_3	$[NHCOC_6H_4OCH_3(p)]o$-	60	148-50	EtOH	$C_{22}H_{16}N_2O_4$	7.5	7.5
Xb_1	$(NHCOC_6H_5)m$-	60	213-15	C_6H_6	$C_{21}H_{14}N_2O_3$	8.1	8.2
Xb_2	$[NHCOC_6H_4CH_3(p)]m$-	65	248-50	EtOH	$C_{22}H_6N_2O_3$	8.0	7.9
Xb_3	$[NHCOC_6H_4CH_3(p)]m$-	66	173-75	EtOH	$C_{22}H_{16}N_2O_4$	7.3	7.5
Xc_1	$(NHCOC_6H_5)p$-	68	>300	C_6H_6	$C_{21}H_{14}N_2O_3$	8.1	8.2
Xc_2	$[NHCOC_6H_4CH_3(op)[p$-	65	278-86	EtOH	$C_{22}H_{16}N_2O_3$	7.9	7.9
Xc_3	$[NHCOC_6H_4OCH_3(p)]p$-	60	>300	AcOH	$C_{22}H_{16}N_2O_4$	7.4	7.5

(*VIa-c*): *Formation of anilides* (*IIIa-n*), *hydrazides* (*IVa-f*), *urea derivatives* (*Va-g, Vh-n and Vo-u*) *and semicarbazides* (*VIIa-f*) (*Table* 1)

Azides IIa-c and/or isocyanates VIa-c (0.1 mol) in dry benzene (20 ml) were treated with aromatic amines (aniline, *p*-toluidine, *p*-anisidine and *p*-chloroaniline), aminobenzoic acids (*o*-, *m*- and *p*-aminobenzoic acids) or the appropriate hydrazine (0.15 mol). The reaction mixture was refluxed for 1 hr, cooled and the solid product filtered and recrystallized from a suitable solvent to give III, IV, V or VII; IR (III and V): 3450-3300 (NH), 1680-1650 (C=O of anilides or diaryl urea)[12], and 1796-1770 and 1720-1710 (C=O coupling bands of cyclic imides); IR (IV): 3340-3220 (NH), 1680-1660 (hydrazide C=O) and 1780-1760 and 1720-1710 (C=O coupling bands of cyclic imides); IR (VII): 3340-3220 (NH), 1700-1650 (semicarbazide C=O)[15], and 1790-1780 and 1715-1710 (C=O coupling bands of cyclic imides).

Hydrolysis of VIa-c with water: *Formation of VIIIa-c* (*Table* 1)

A solution of VI (0.1 mol) in benzene (20 ml) was treated with a little amount of distilled water (2 ml) and the reaction mixture refluxed for 1 hr. The separated solid was filtered and recrystallized from a suitable solvent to give VIII; IR: 3340-3300 (NH), and 1730-1770 and 1720-1710 (C=O of diarylureas)[12].

Action of aromatic substrates on azides (*IIa-c*) *and/or isocyanates* (*VIa-c*) *in the presence of anhyd.* $AlCl_3$: *General procedure*

Anhyd. $AlCl_3$ (0.3 mol) was added with stirring to IIa-c and/or VIa-c (0.1 mol) in dry aromatic substrate at room temperature. The reaction mixture was stirred for 1 hr, and the resulting complex decomposed with ice-water/cold dil. HCl. The excess of solvent was steam-distilled and the residual solid filtered and recrystallized from a suitable solvent to give IX and/or X; IR (IX): 1780-1760 (C=O of aromatic ketones)[5], and 1780-1750 and 1720-1710 (C=O of cyclic imides); IR(X): 3350-3300 (NH), 1680-1650 (C=O of anilides)[6] and 1790-1770 and 1710-1715 (C=O of cyclic imides).

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A Facile & New Route for the Synthesis of Substituted 1,2-Dithiafulvenes Using Phosphonium Ylides

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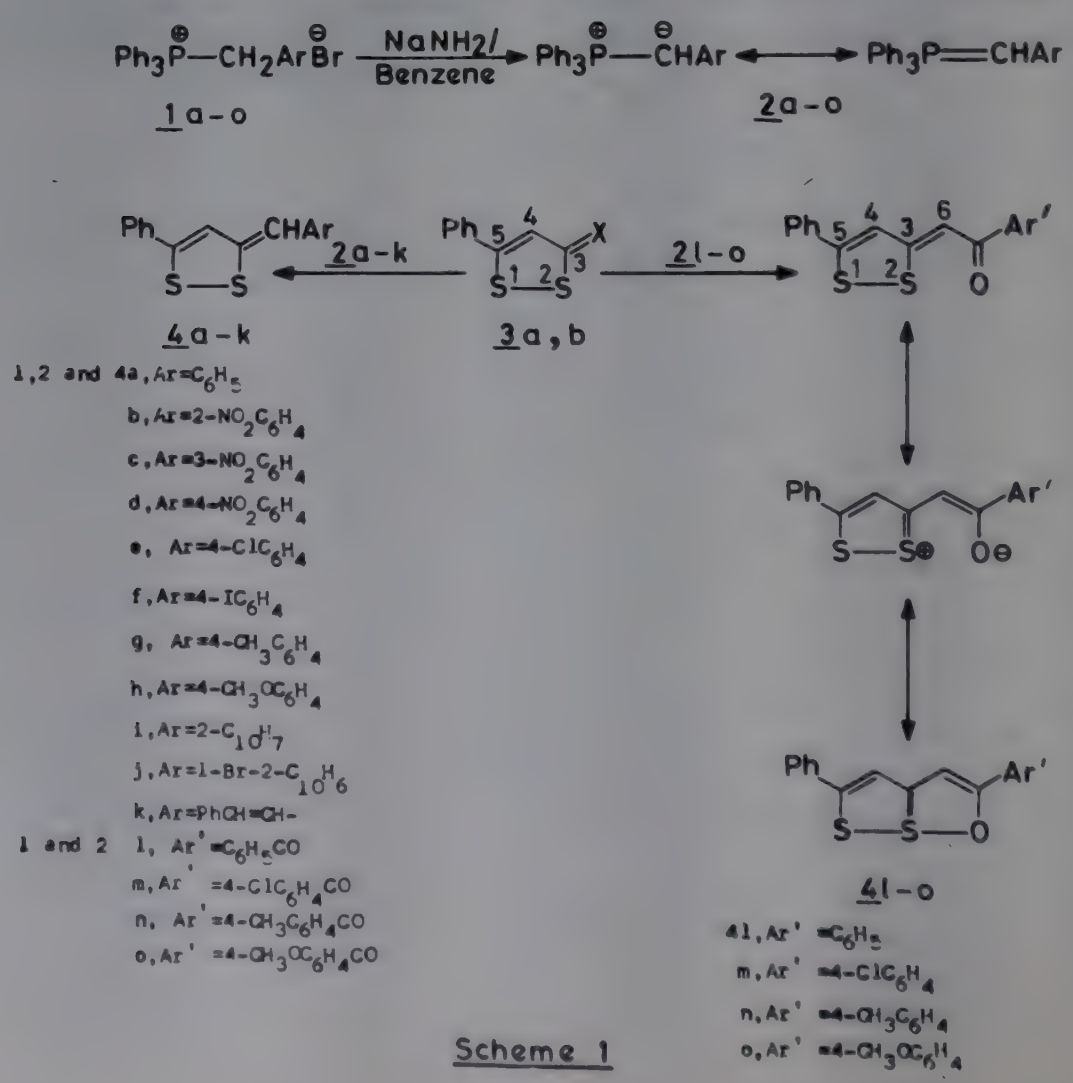
A wide variety of 6-aryl-5-phenyl-1,2-dithiafulvenes and 6-aroyl-5-phenyl-1,2-dithiafulvenes (**4**) have been synthesized by the interaction of 5-phenyl-1,2-dithiol-3-one (**3a**) and phosphonium ylides (**2**). The synthesis of these dithiafulvenes has also been carried out by an alternative route involving the condensation of **2** with 5-phenyl-1,2-dithiole-3-thione (**3b**). The spectral data are consistent with the proposed structures for the products.

Many routes have been devised to introduce the exocyclic double bond at C-3 position of 1,2-dithiole ring to form substituted 1,2-dithiafulvenes[1-5]. However, these methods were found to be less versatile because of drastic reaction conditions and formation of rearranged products alongwith the desired ones. Therefore, a great need still exists for a versatile and facile route to synthesize substituted 1,2-dithiafulvenes (**2a-k**) with 5-phenyl-1,2-dithiol-3-one (**3a**) and 5-under simpler conditions. We wish to report herein a convenient and new route for the synthesis of some substituted 1,2-dithiafulvenes (**4**) via the interaction of phosphonium ylides (**2**) with 5-phenyl-1,2-dithiol-3-one (**3a**) and 5-phenyl-1,2-dithiole-3-thione (**3b**).

Quaternization of triphenylphosphine with substituted benzyl bromides, 2-bromomethylnaphthalene, 1-bromo-2-bromomethylnaphthalene, cinnamyl bromide and substituted phenacyl bromides at reflux temperature gave substituted (benzyl)triphenylphosphonium bromides (**1a-h**), (2-naphthylmethyl)triphenylphosphonium bromides (**1i-j**), (cinnamyl)triphenylphosphonium bromide (**1k**) and (phenacyl)triphenylphosphonium bromides (**1l-o**) in good yields. Treatment of these phosphonium salts (**1a-o**) with sodamide or sodium hydride in benzene effected proton abstraction yielding the corresponding ylides, viz. substituted (benzylidene)triphenylphosphoranes (**2a-h**), (2-naphthylmethylene)triphenylphosphoranes (**2i-j**), (cinnamylidene)triphenylphosphorane (**2k**) and (phenacylidene)triphenylphosphoranes (**2l-o**) (Scheme 1).

The reaction of semi-stabilized phosphonium ylides



Scheme 1

phenyl-1,2-dithiolethione (**3b**) was carried out at room temperature to give 5-phenyl-6-substituted-aryl-1,2-dithiafulvenes(3-arylidene-5-phenyl-1,2-dithioles) (**4a-k**) (Scheme 1) in 40-80% yields.

However, reaction of carbonyl-stabilized ylides, (*p*-substituted-phenacylidene)triphenylphosphoranes (**2l-o**) with **3a** or **3b** gave 5-phenyl-6-substituted-1,2-dithiafulvenes (5-phenyl-3-substituted-phenacylidene-1,2-dithioles) (**4l-o**; Scheme 1) in 50-80% yields.

The ketone **3a** was found to be more reactive than the thioketone **3b** since the former when condensed with ylides **2a-o** afforded the products **4a-o** in better yields. It was also interesting to note that the position of substituent in the dithiole ring had a great effect in carbonyl olefination. Thus, 4-phenyl-1,2-dithiole-3-thione (**3b**) failed to couple with the phosphonium ylides **2a-o**, probably due to steric hindrance caused by phenyl ring.

Melting points of all the 1,2-dithiafulvenes (**4a-o**; Table 1) prepared by the olefination of the ketone **3a**, were very close to those prepared by olefination of the thioketone **3b**. The IR(KBr) spectra of **4a-k** showed

Table 1—Physical Data of 3-Arylidene-5-phenyl-1,2-dithioles (**4a-o**)

Compd	Ar	m.p. °C	Yield (%) via route		Crystallized from	Found (%) (Calc.)		PMR (δ, ppm)
			A	B		C	H	
4a	C_6H_5	134-36	80	65	EtOH	71.6 (71.6	4.4 4.5)	--
4b	2-$NO_2C_6H_4$	128-30	70	60	C_6H_6-hexane	61.3 (61.3	3.5 3.5)	--
4c	3-$NO_2C_6H_4$	230-32	65	52	EtOH	61.3 (61.3	3.5 3.5)	—
4d	4-$NO_2C_6H_4$	142-44	86	75	$CHCl_3$-pet. ether	61.3 (61.3	3.5 3.5)	7.16 (*s*, 1H, Ar−C*H*=C<), 7.19 (*s*, 1H, >C=C*H*−), 7.20-8.20 (*m*, 9H, Ar−*H*)
4e	4-ClC_6H_4	155-58	58	40	EtOH	63.5 (63.5	3.7 3.6)	7.27 (*s*, 1H, Ar−C*H*=C<), 7.34 (*s*, 1H, >C=C*H*−), 7.36-7.90 (*m*, 9H, Ar−*H*)
4f	4-IC_6H_4	148-50	50	45	EtOH	48.7 (48.8	2.8 2.8)	7.40 (*s*, 1H, Ar−C*H*=C<), 7.44 (*s*, 1H, >C=C*H*−), 7.52-8.50 (*m*, 9H, Ar−*H*)
4g	4-$CH_3C_6H_4$	112-14	45	35	$CHCl_3-C_6H_6$	72.3 (72.3	4.9 4.9)	7.14 (*s*, 1H, Ar−C*H*=C<), 7.20 (*s*, 1H, >C=C*H*−), 2.38 (*s*, 3H, −C*H*$_3$), 7.22-8.00 (*m*, 9H, Ar−*H*)
4h	4-$CH_3OC_6H_4$	148-50	65	50	EtOH	68.4 (68.5	4.7 4.7)	6.82 (*s*, 1H, Ar−C*H*=C<), 7.00 (*s*, 1H, >C=C*H*−), 3.83 (*s*, 3H, OC*H*$_3$), 7.20-8.10 (*m*, 9H, Ar−*H*)
4i	2-$C_{10}H_7$	140	70	50	$CHCl_3$-hexane	75.4 (75.5	4.4 4.4)	7.33 (*s*, 1H, Ar−C*H*=C<), 7.35 (*s*, 1H, >C=C*H*−), 7.38-7.93 (*m*, 12H, Ar−*H*)
4j	1-Br-2-$C_{10}H_6$	258-60	50	40	EtOH	60.5 (60.5	3.3 3.3)	—
4k	$C_6H_5CH=CH-$	128-30	60	50	EtOH	73.5 (73.5	4.7 4.8)	—
4l	C_6H_5CO-	128-30	60	50	EtOH	71.4 (71.3	4.1 4.1)	—
4m	4-ClC_6H_4CO	130-32	55	50	$CHCl_3$-pet. ether	63.7 (63.7	3.7 3.7)	—
4n	4-$CH_3C_6H_4CO$	112-14	60	50	Benzene	69.6 (69.7	4.5 4.5)	7.23 (*s*, 1H, Ar−C*H*=C<), 7.25 (*s*, 1H, >C=C*H*−), 2.40 (*s*, 3H, −C*H*$_3$), 7.30-8.10 (*m*, 9H, Ar−C*H*)
4o	4-$CH_3OC_6H_4CO$	97-98	80	70	$CHCl_3$−EtOH	66.3 (66.3	2.3 2.3)	6.78 (*s*, 1H, Ar−C*H*=C<), 6.93 (*s*, 1H, >C=C*H*−), 3.85 (*s*, 1H, −OC*H*$_3$), 7.04-8.13 (*m*, 9H, Ar−C*H*)

Route-A forms the reaction between **2** and **3a** and route-B between **2** and **3b**.

absorption bands at 1605-1585 ($\nu C=C$) and 970-958 cm^{-1}. The latter absorption bands were associated with the out-of-plane deformations of the hydrogen atom attached to a carbon-carbon double bond[8]. In the case of compounds **4l-o**, the carbonyl stretching bands were strong and appeared at 1520-1620 instead of appearing in the usual range[9] (1720-1620 cm^{-1}). The PMR($CDCl_3$) spectra of **4** in general exhibited olefinic protons at δ 6.80-7.40, olefinic protons of dithiole ring at 7.00-7.45 and aromatic protons at 7.20-8.50 (Table 1).

All the reagents were procured from commercial sources (BDH and E. Merck). The ketone **3a** and the thioketone **3b** were prepared by the method reported in the literature[10]. All the phosphonium salts (**1a-o**) were prepared by heating triphenylphosphine with substituted alkyl halides in anhyd benzene at reflux temperature[11-14].

6-*Aryl*-5-*phenyl*-1,2-*dithiafulvenes* (**4a-k**)

To a stirred suspension of ylide (**2a-l**), generated from **1a-k** (4 mmol) and sodamide (5 mmol) in anhyd benzene (100 ml) was added dropwise a solution of **3a** or **3b** (4 mmol) in benzene (20 ml) during 30 min. The mixture was stirred at room temperature for 6-12 hr and the residue containing triphenylphosphine oxide and unreacted sodamide filtered. The filtrate was concentrated on a steam-bath under reduced pressure.

The resulting mass was chromatographed over neutral alumina using pet ether (40-60°)-benzene (1:2) as eluent to give **4** which was recrystallized from an appropriate solvent (Table 1).

6-*Aroyl*-5-*phenyl*-1,2-*dithiafulvenes* (**4l-o**)

To a mixture of **1l-o** (4 mmol) and sodamide (5 mmol) in anhyd. benzene (100 ml), was added under nitrogen atmosphere, the ketone **3a** or **3b** (4 mmol). The mixture was refluxed for 8-16 hr and left overnight. The residue was filtered off and the filtrate evaporated on a steam-bath. The resulting mass was chromatographed using pet. ether-benzene (1:1) as eluent to give the desired product (**4l-o**) in 60-80% yield which recrystallized from a suitable solvent (Table 1).

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Condensed Heterocyclics: Part XVIII – Substitution Reactions of 1,2,5-Thiadiazolo[3,4-*c*]- & 1,2,5-Selenadiazolo[3,4-*c*]-quinolines

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1,2,5-Thiadiazolo[3,4-*c*]- and 1,2,5-selenadiazolo-[3,4-*c*]-quinolines (I) have been oxidised with *m*-chloroperbenzoic acid to the corresponding N^4-oxides (II). Electrophilic and nucleophilic substitution reactions of I and II have been studied.

Synthesis of 1,2,5-thiazolo[3,4-*c*]-(Ia) and 1,2,5-selenadiazolo[3,4-*c*]-quinolines (Ib) has been reported recently[1] from this laboratory. In view of the biological activity of 1,2,5-thiadiazole[2], 1,2,5-selenadiazole[3] and quinoline[4] moieties it was thought worthwhile to prepare derivatives of the parent compounds by their electrophilic and nucleophilic substitution reactions as well as by carrying out such reactions on their N^4-oxides.

1,2,5-thiadizolo[3,4-*c*]quinoline (Ia) was treated with *m*-chloroperbenzoic acid in methylene chloride at 0-5° to get only 1,2,5-thiadiazolo[3,4-*c*]quinoline-N-oxide (IIa). A similar treatment of 1,2,5-selenadiazolo-[3,4-*c*]quinoline (Ib) gave 1,2,5-selenadiazolo[3,4-*c*]quinoline-N-oxide (IIb). The N-oxides (IIa, b) (Table 1) were characterised by their IR and PMR spectral data. The upfield shift of C_4-proton (Table 2) confirmed the formation of N-oxides.

Ia on nitration with fuming nitric acid in conc. sulphuric acid gave a nitro compound as evidenced by the presence of bands at 1540 and 1350 cm^{-1} in its IR spectrum. However, its PMR spectrum showed it to be a mixture of 9-nitro (IIIa) and 6-nitro-1,2,5-thiadiazolo[3,4-*c*]quinolines (IVa) in the ratio 2 : 1. The chemical shifts for the benzene protons of IIIa and IVa were calculated taking the deshielding effects of nitro group on *ortho*-, *meta*- and *para*-positions[5] to be δ 0.95, 0.17 and 0.33 respectively, and also to be additive. The calculated values were comparable with the observed chemical shifts (Table 3). All attempts to resolve the mixture proved abortive. However, due to high susceptibility of selenium to nitric acid, attempts

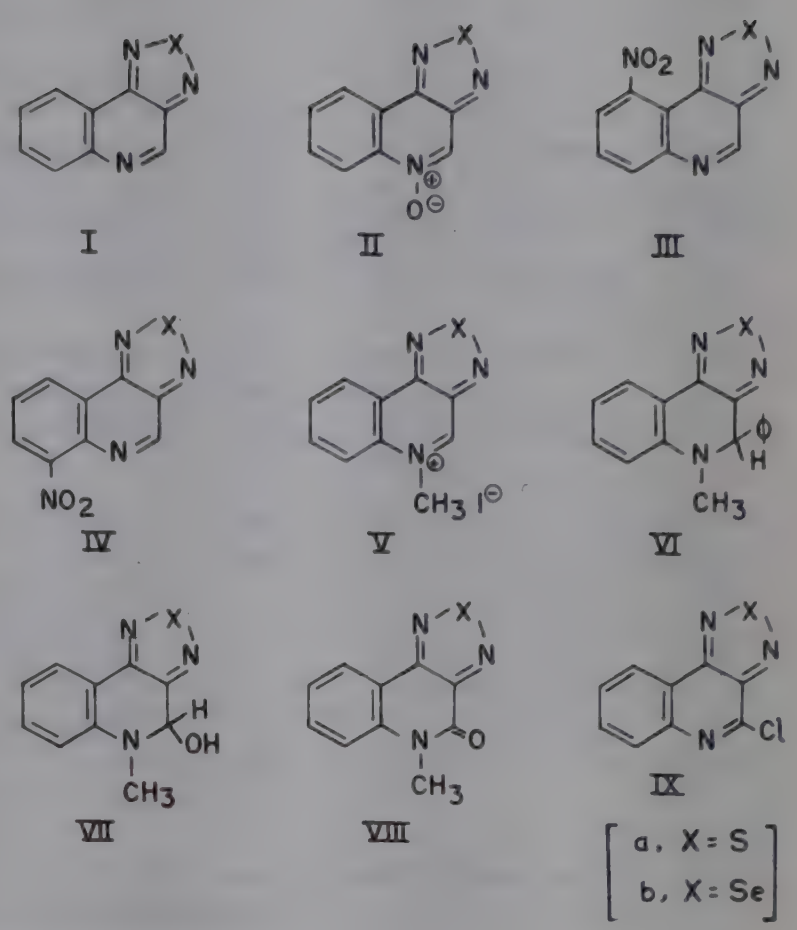

Table 1 – Characterization Data of Various 1,2,5-Thiadiazolo[3,4-*c*]- and 1,2,5-Selenadiazolo[3,4-*c*]-quinolines

Compd	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.)		
				C	H	N
IIa	60	121-22	$C_9H_5N_3SO$	53.1(53.2)	2.2(2.5)	21.2(20.7)
IIb	74	215-16	$C_9H_5N_3SeO$	43.1(43.4)	2.0(2.0)	16.7(16.9)
Va	87	224-25	$C_{10}H_8N_3IS$	45.2(45.2)	2.8(3.0)	15.7(15.8)
Vb	72	204-5	$C_{10}H_8N_3ISe$	31.8(32.0)	2.3(2.2)	11.4(11.2)
VIa	58	56-7	$C_{16}H_{13}N_3S$	68.4(68.8)	4.2(4.6)	15.3(15.0)
VIIa	45	92-3	$C_{10}H_9N_3SO$	54.7(54.8)	3.9(4.1)	19.2(19.2)
VIIb	34	160-61	$C_{10}H_9N_3SeO$	45.0(45.3)	3.1(3.4)	15.9(15.9)
VIIIa	75	177-78	$C_{10}H_7N_3SO$	54.9(55.3)	3.4(3.2)	19.2(19.4)
VIIIb	74	220-21	$C_{10}H_7N_3SeO$	45.8(45.6)	2.5(2.7)	15.8(16.0)
IXa	57	123-24	$C_9H_4N_3SCl$	48.6(48.8)	1.6(1.8)	18.7(19.0)
IXb	38	167-68	$C_9H_4N_3SeCl$	40.3(40.39)	1.6(1.5)	15.5(15.7)

Table 2 – PMR Spectral Analysis of 1,2,5-Thiadiazolo[3,4-*c*]- and 1,2,5-Selenadiazolo[3,4-*c*]-quinolines (Chemical Shifts in δ, ppm)

Compd	Solvent	H-4	H-6	H-7 H-8	H-9	6N – Me	4-OH or 4-C_6H_5	*J* values (Hz)
Ia[1]	$CDCl_3$	9.42 (*s*)	8.18 (*dd*)	←7.72 to 7.80→	8.62 (*dd*)	—	—	$J_{8,9}=J_{6,7}=9.0$; $J_{7,9}=J_{6,8}=2.5$
Ib[1]	DMSO-d_6	9.20 (*s*)	7.95 (*dd*)	←6.65 to 7.70→	8.47 (*dd*)	—	—	$J_{8,9}=J_{6,7}=9.0$; $J_{7,9}=J_{6,8}=2.5$
IIa	DMSO-d_6	9.32 (*s*)	8.65 (*dd*)	7.85 to 7.53	8.05 (*dd*)	—	—	$J_{8,9}=J_{6,7}=J_{7,8}=8.5$; $J_{7,9}=2.5$
IIb	DMSO-d_6	9.05 (*s*)	8.60 (*dd*)	←8.20 to 7.80→	8.53 (*dd*)	—	—	$J_{8,9}=J_{6,7}=8.5$; $J_{7,9}=2.5$
VIa	$CDCl_3$	2.20 (*s*)	7.48 (*dd*)	←7.40 to 7.05→	7.55 (*dd*)	1.30 (*s*)	7.40 to 7.05(C_6H_5)	$J_{8,9}=J_{6,7}=9.0$; $J_{7,8}=8.0$
VIIa	DMSO-d_6	3.80 (*s*)	7.45 (*dd*)	←7.10 to 6.50←	7.95 (*dd*)	3.00 (*s*)	4.70 (OH)	$J_{8,9}=J_{6,7}=9.0$; $J_{7,8}=8.0$; $J_{7,9}=J_{6,8}=3.5$
VIIb	$CDCl_3$/TFA	4.60 (*s*)	7.40 (*dd*)	←7.05 to 6.65→	8.05 (*dd*)	3.08 (*s*)	4.60 (OH)	$J_{8,9}=J_{6,7}=9.0$; $J_{6,8}=J_{7,9}=3.5$
VIIIa	$CDCl_3$	—		←7.70 to 7.20→	8.27 (*dd*)	3.74 (*s*)	—	$J_{8,9}=8.0$; $J_{7,9}=2.0$
IXa	$CDCl_3$	—		←8.20 to 7.60→	8.53 (*dd*)	—	—	$J_{8,9}=8.0$; $J_{7,9}=2.0$
IXb	$CDCl_3$/TFA	—	8.05 (*dd*)	←7.60 to 7.30→	8.35 (*dd*)	—	—	$J_{8,9}=J_{6,7}=8.5$; $J_{7,9}=J_{6,8}=3.0$

Table 3 – Observed and Calculated Chemical Shifts* (in δ scale) for the Various Benzene Protons of 9-Nitro- and 6-Nitro-1,2,5-thiadiazolo[3,4-*c*]quinolines (IIIa and IVa)

Compd	H-6		H-7		H-8		H-9	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
IIIa	8.45	8.51	7.85	7.89	8.80	8.75	—	—
IVa	—	—	8.65	8.67	8.17	7.97	8.90	8.95

* Chemical shifts were calculated by adding the deshielding values of nitro group on *o*-, *m*- and *p*-protons to the chemical shifts due to H-6, H-7, H-8 and H-9 of Ia.

to nitrate Ib under similar conditions were unsuccessful and not even a trace of IIIb and/or IVb could be obtained.

Compounds Ia and Ib on treatment with methyl iodide in dry benzene gave the methiodides Va and Vb respectively. The methiodide Va when treated with freshly prepared phenyl magnesium bromide afforded 4,5-dihydro-5-methyl-4-phenyl-1,2,5-thiadiazolo[3,4-*c*]quinoline (VIa). However, the selenium analogue (Vb) on similar reaction did not give the desired compound (VIb).

Compounds Ia and Ib were treated with 10% ethanolic potassium hydroxide under reflux to give 4,5-dihydro-4-hydroxy-N^5-methyl-1,2,5-thiadiazolo[3,4-*c*]- (VIIa) and 4,5-dihydro-4-hydroxy-N^5-methyl-1,2,5-selenadiazolo[3,4-*c*]-quinolines (VIIIb) respectively. Their IR and PMR spectra confirmed that these compounds, although expected to be tautomeric mixtures, existed only in hydroxy forms.

The methiodides Va and Vb when oxidised with alkaline potassium ferricyanide gave 4,5-dihydro-N^5-methyl-4-oxo-1,2,5-thiadiazolo[3,4-*c*]- (VIIIa) and 4.5-dihydro-N^5-methyl-4-oxo-1,2,5-selenadiazolo-[3,4-*c*]- quinolines (VIIIb), respectively.

Compound VIIIa when treated with PCl_5 in molten *p*-dichlorobenzene gave 4-chloro-1,2,5-thiadiazolo-[3,4-*c*]-quinoline (IXa). However, the selenium analogue (VIIIb) failed to give the desired 4-chloro compound (IXb) under identical conditions.

The N^4-oxide IIb on similar treatment with $POCl_3$ gave 4-chloro-1,2,5-selenadiazolo[3,4-*c*]quinoline (IXb).

The structures of the compounds were elucidated by their IR and PMR spectral analysis. The PMR spectra (cf. Table 1), showed uniform trend in going from sulphur to selenium analogue as has been reported by earlier workers[6,7].

Melting points are uncorrected. IR spectra were recorded on a Beckmann IR-20 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra on a Perkin-Elmer R-32 spectrometer (chemical shifts in δ, ppm downfield from TMS).

1,2,5-*Thiadiazolo*[3,4-*c*]*quinoline-N*^{5}-*oxide* (*IIa*; *Table* 1)

A solution of Ia (1.87 g; 0.01 mol) in dry CH_2Cl_2 was cooled to 0-5° and *m*-chloroperbenzoic acid (3.4 g; 0.02 mol) in dry CH_2Cl_2 (15 ml) added dropwise to it with vigorous stirring keeping the temperature of the reaction mixture below 0°. After the addition was over (*ca.* 1 hr), the reaction mixture was stirred for 30 min, refluxed on a water-bath for another 30 min, rendered saturated with ammonia and filtered. The solvent was stripped off and the usual work-up followed by chromatography over silica gel afforded IIa; IR (KBr): 1240 (N→O), 1610 (C=N).

The characterization data of the selenium analogue prepared in a similar manner are given in Table 1.

9-*Nitro- and* 6-*nitro*-1,2,5-*thiadiazolo*[3,4-*c*]-*quinolines* (*IIIa and IVa*):

A solution of Ia (8.45 g; 0.0025 mol) in a minimum quantity of conc. H_2SO_4 (*ca.* 10 ml) at 0° was stirred well, cooled and fuming HNO_3 (5 ml) added to it in small portions so as to maintain the temperature below 0°. The stirring was continued further for 1 hr at room temperature and the reaction mixture finally heated on a water-bath for 1 hr, cooled, poured into ice-cold water (100 ml), basified with ammonia solution and extracted with chloroform. The extract was dried (Na_2SO_4) and on usual work-up and column chromatography provided an unresolvable mixture of IIIa and IVa (0.34 g; 59%), m.p. 150-56° (Found: C, 46.2; H, 1.4; N, 25.1. $C_9H_4N_4O_2S$ requires C, 46.6; H, 1.7; N, 24.3%); IR (KBr): 1620 (C=N), 1540, 1350 (NO_2), 1490 (ring breathing).

1,2,5-*Thiadiazolo*[3,4-*c*]*quinoline metthiodide* (*Va*; *Table* 1)

Excess of freshly distilled CH_3I (5 ml) was added to a solution of Ia (0.93 g; 0.005 mol) in dry benzene (25 ml), the reaction mixture refluxed on a water-bath for 4 hr under anhydrous conditions and allowed to stand overnight. The precipitated red coloured methiodide (Va) was filtered, washed with dry benzene and dried *in vacuo*; IR (KBr): 1620 (C=N).

Methiodide Vb (Table 1) was prepared in a similar way.

4,5-*Dihydro*-5-*methyl*-4-*phenyl*-1,2,5-*thiadiazolo*-[3,4-*c*]*quinoline* (*VIa*; *Table* 1)

To the freshly prepared phenylmagnesium bromide was added Va (0.66 g; 0.0025 mol) when a vigorous reaction ensued. After the reaction subsided, the reaction mixture was refluxed on a water-bath for 1 hr, solvent removed, the residue added to water (60 ml) and the organic material taken up in chloroform. The aqueous layer was washed with chloroform (2 × 50 ml) and the combined extracts were washed with water and dried (Na_2SO_4). The solvent was stripped off and the residue after usual work-up and column chromatography afforded TLC-pure white coloured VIa with characteristic smell; IR (KBr): 1620 (C=N).

4,5-*Dihydro*-4-*hydroxy*-5-*methyl*-1,2,5-*thiadiazolo*[3,4-*c*]*quinoline* (*VIIa*; *Table* 1)

Methiodide Va (0.66 g; 0.0025 mol) was treated with 10% ethanolic KOH (15 ml) and the contents were refluxed on a water-bath for 6 hr. After cooling, the reaction mixture was poured in ice-cold water (100 ml) and the aq. layer extracted with chloroform, dried (Na_2SO_4), worked-up as usual and column chromatographed to afford the TLC-pure red compound VIIa; IR (nujol): 3200 (br, OH).

The selenium analogue (VIIa; Table 1) was prepared in a similar manner.

4,5-*Dihydro*-5-*methyl*-4-*oxo*-1,2,5-*thiadiazolo*[3,4-*c*]*quinoline* (*VIIIa*; *Table* 1):

Potassium ferricyanide (2.5 g) in water (40 ml) was added to Va (0.7 g; 0.0025 mol) water (100 ml) and ether (100 ml). The mixture was stirred for 1.5 hr, and 10% KOH added to it dropwise until the solution became alkaline. After 15 min, the ether layer was separated, and the aq. layer with suspended material taken up in chloroform. The combined ether and chloroform layers were washed with water, dried (Na_2SO_4), worked-up as usual and column chromatographed to give VIIIa; IR (nujol): 1670 (C=O), 1610 (C=N).

The selenium analogue (VIIIb; Table 1) was prepared in a similar manner.

4-*Chloro*-1,2,5-*thiadiazolo*[3,4-*c*]*quinoline* (*IXa*; *Table* 1)

To VIIIa (0.43 g; 0.002 mol), *p*-dichlorobenzene (0.8 g) and PCl_5 were added and the reaction mixture was heated in a sealed tube at 230-40° for 6 hr, cooled and solid product finally ground and triturated with etherial hydrochloric acid. The resultant hydrochloride was filtered, suspended in water and the suspension made alkaline with 5% NaOH solution. The aq. layer was extracted with chloroform (100 × 2ml) and the combined organic layers were washed with water and dried (Na_2SO_4). Evaporation of the solvent and column chromatography afforded IXa as a white coloured compound; IR (nujol): 820 (C−Cl).

4-Chloro-1,2,5-selenadiazolo[3,4-c]quinoline (*IXb*; *Table* 2)

Compound IIb (0.498 g; 0.002 mol) was refluxed with excess of $POCl_3$ (8 ml) for 3 hr, cooled, poured into cold water and basified with ammonia. The organic material was taken up in chloroform and the aqueous layer extracted with chloroform (2 × 75 ml). The combined chloroform extracts were washed with water and dried (Na_2SO_4). Usual work-up including column chromatography gave IXb.

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Formation of a Cyclic Sulphenic Ester during Photochemical Decomposition of 2,5-Diphenyl-1,4-dithiin-1-oxide—A Novel Case of Ring Expansion

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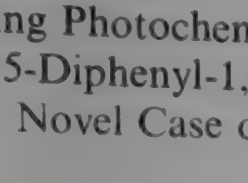
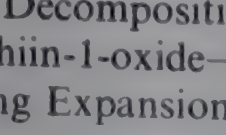
Photolysis of 2,5-diphenyl-1,4-dithiin-1-oxide (I) at 2537Å in DMSO affords the ring enlarged product, 4,7-diphenyl-2,5-dithiaxepin (II). The structural assignment of II is based on elemental analysis and spectral data (IR, UV, PMR and mass).

It has been shown that sulphenate esters play an important role in the photoracemization of sulphoxides[1]. Evidence for the clean extrusion of SO moiety from sulphoxides under photolytic conditions either in the presence or absence of sensitizers is, however, lacking[2-4]. In most cases rearrangement is found to take place. The photochemical rearrangement of sulphoxides to sulphenic ester has been invoked in several cases[5,6]. This prompted the author to study the photochemical decomposition of 2,5-diphenyl-1,4-dithiin-1-oxide (I) in the absence of sensitizer. The photochemical decomposition of I is found to give a highly complex mixture of products from which it has been possible to isolate 4,7-diphenyl-2,5-dithiaoxepin (II), albeit in poor yield (4%).



(I)



(II)

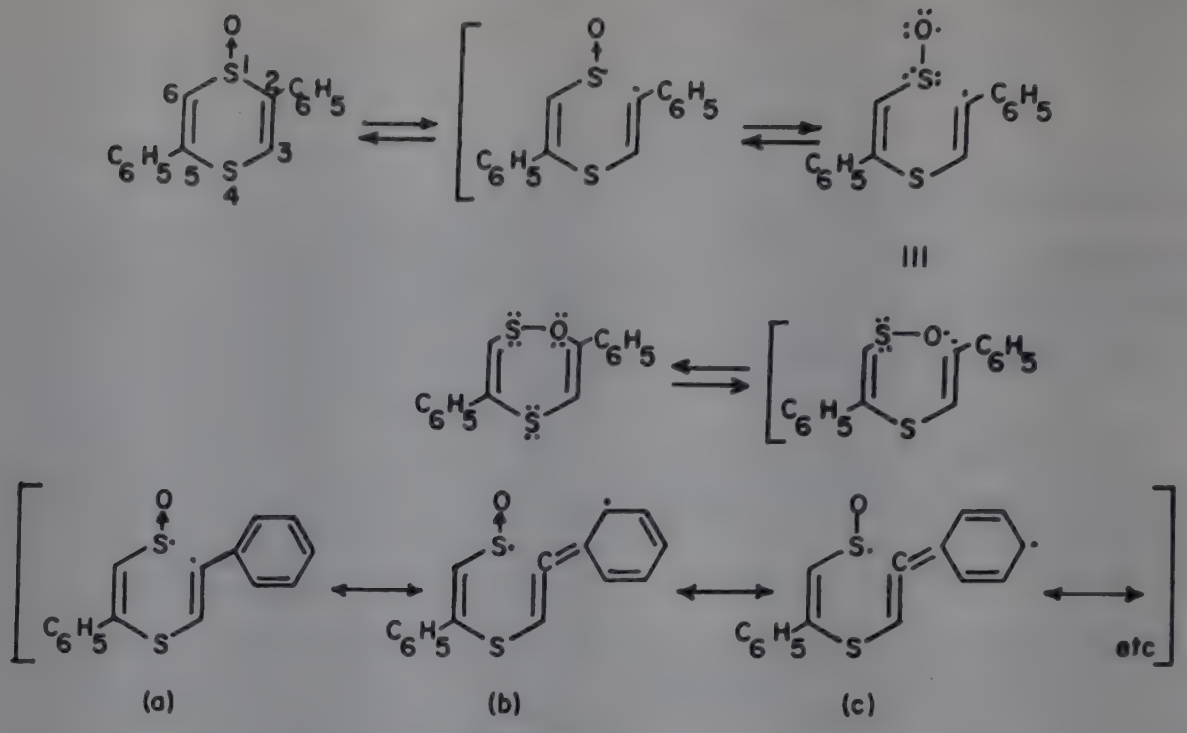
In order that the results of photolysis are not vitiated by those of thermal dethionylation paths, the reaction mixture was maintained at relatively low temperature (25-27°C)[7]. The photolysis of I was relatively slow in methanol since unreacted sulphoxides could be recovered (column chromatography) to the extent of 50% after 11 hr of exposure at 2537Å. During the reaction in methanol a solid product was found to be deposited on the walls of the quartz reactor and stirring was ineffective in preventing the formation of this coating. Due to the filtering action of the latter the reaction in methanol was further slowed down. In order to prevent this difficulty DMSO was chosen as the solvent.

When photolysis of I was carried out in DMSO in a Rayonet photochemical reactor (RPR-100) at 2537Å under nitrogen atmosphere at 25-27°C the colour of the solution changed from colourless to yellow within 2 min. The photolysis was complete (TLC) on irradiation for 11 hr. The extended period of irradiation was attended by the formation of secondary photolytic products. The complexity of the reaction for the photolysis of a relatively simple sulphoxide such as dibenzyl sulphoxide rendered even the prediction of the photolytic decomposition products of I very difficult. In spite of these difficulties and inability to account for the recovery of the major part of the starting material some significant results have been obtained.

The clue to the understanding of the photochemical reaction path was the isolation, albeit in only 4% yield of hitherto unreported seven-membered heterocyclic dithiaoxepin in the form of a bright yellow solid, m.p. 147-49° (d). It analysed for $C_{16}H_{12}S_2O$ (M^+ 284) (Found: C, 67.7; H, 4.1; S, 22.5. $C_{16}H_{12}S_2O$ requires C, 67.6; H, 4.3; S, 22.5%) and exhibited in its IR spectrum in KBr peaks at 3090, 3070, 3030, 1695, 1490, 1450, 690 and 650 cm^{-1}. Its UV spectrum in ethyl acetate exhibited maximum absorptions at 253 (ε 18465), 317 (6036) and 390 nm (1526, br). The PMR spectrum of this solid in $CDCl_3$ (chemical shifts in δ-scale, downfield from TMS internal standard) displayed two singlets of one-proton each at δ 6.15 and 6.20, assignable to olefinic protons, and a ten-proton multiplet in the region 7.35-8.0 assignable to aromatic protons.

The absence of $\nu S \rightarrow O$ around 1060 cm^{-1} and its insolubility in polar solvents like methanol and 95% ethanol eliminated the possibility of sulphoxide structure isomeric with the starting material, i.e. structure resulting from a migration of a phenyl group or even the episulphexidic valence tautomer suggested as an intermediate in the thermal dethionylation. The presence of only one oxygen in the molecule and the absence of IR bands in the regions 1140-1160 and 1300-1350 cm^{-1} ruled out the possibility of its being a sulphone. The corresponding sulfone of I did not decompose at the melting point of 147-49°. All these evidences suggested structure (II) for this photolysis product.

The formation of the sulfenate ester (II) probably occurs by (1,2) carbon-sulphur bond cleavage involving a diradical as shown in Scheme 1. The odd electron generated in the olefinic carbon can be thought to be better stabilized by the phenyl ring attached to it giving



Scheme I

rise to the various resonance stabilized structures such as (a), (b), (c) etc. (see Scheme 1). This will not be the case if (1,6) C – S bond cleavage occurs. The possibility of formation of another cyclic sulphenic ester isomeric to II, suggested as an intermediate during the formation of 1,3-dithiols from 1,4-dithiin sulphoxide under conditions[8], can not be ruled out. The cleavage of (4,5) C – S bond may also compete with the cleavage of (1-2) C – S bond. Such cleavage may, however, lead to structurally more complicated molecules.

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Allylic Oxidation of Methyl *trans*-2-Octadecenoate by Chromium Trioxide

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The products formed during the preparation of methyl 4-oxo-*trans*-2-octadecenoate (II) from the reaction of methyl *trans*-2-octadecenoate (I) with chromium trioxide have been characterized as monoketo derivatives of hexadecanoic acid (III) and methyl 4-oxo-*trans*-2-octadecenoate (IV). The relative amounts and the structure elucidation of these keto derivatives are based on their mass spectral data.

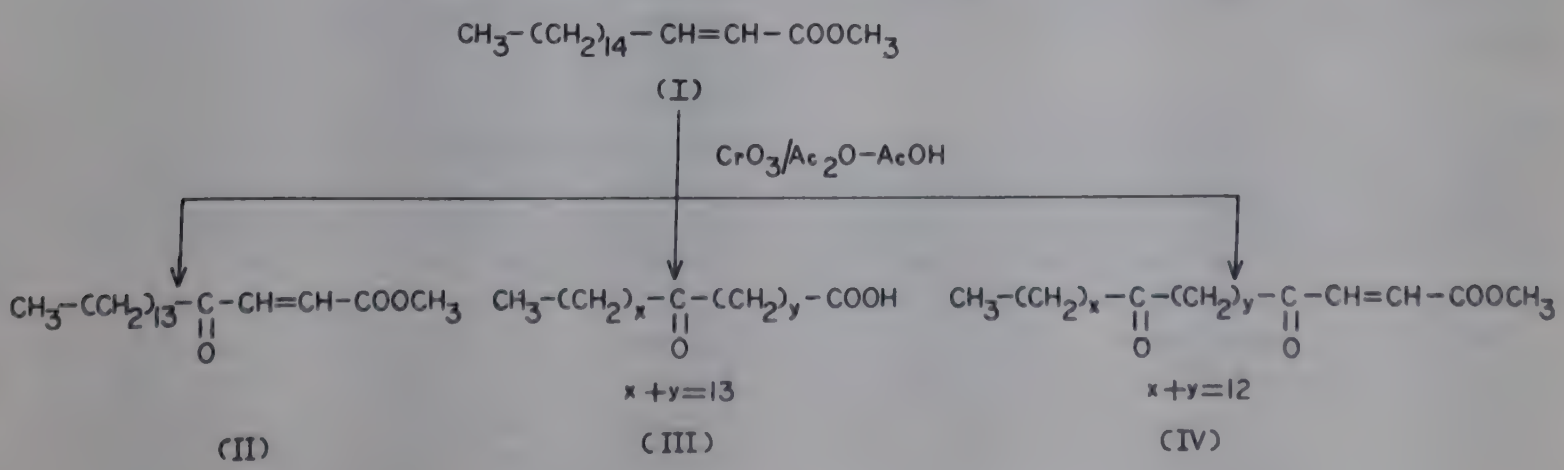
Chromium trioxide in acetic acid has been found to be very efficient reagent for the allylic oxidation of alkenes[1]. Recently Nakayama *et al.*[2] have exploited this reagent more successfully with methyl 2-alkenoates and reported the formation of methyl 4-oxo-2-alkenoates as a sole product in many of the reactions. The side product observed in few cases has been a simple carboxylic acid, resulting from the cleavage of olefinic linkage. No remote oxidation, isomerisation or double bond migration products have been shown in these reactions. However, the direct remote conversion of methyl stearate and homologous esters into monoketo derivatives by chromium trioxide has been described by Eck and coworkers[3]. These authors identified the positions of keto function at unactivated but conformationally favoured centres in the molecules by a study of their mass spectrometry.

In this note we report the results of the allylic oxidation of methyl *trans*-2-octadecenoate (I) with special emphasis on the study of remote oxidation products. The results were further substantiated by extending the work on methyl *trans*-2-hexadecenoate and methyl *trans*-2-docosenoate.

The allylic oxidation of I with chromium trioxide, carried out according to the procedure of Nakayama *et al.*[2], gave the expected methyl 4-oxo-*trans*-2-octadecenoate (II) along with the two unusual minor products (III, IV). In fact, such type of the co-products, having higher R_f values than those of the substrates and responding to DNP test positively, have not been yet reported in the allylic oxidation stydies[1,2]. The compound II showed similar chromatographic and spectral (UV, IR, PMR) characteristics as described earlier[4]. A study of its mass spectrum confirmed the structure as shown in Scheme 1.

The compound III, obtained in a low yield, was identified as a carboxylic acid having a mid-chain carbonyl function on the basis of IR [1715 (C=O), 1705 cm^{-1} (COOH)] and PMR [δ 2.28 (6H, $-CH_2-CO-CH_2-$, $-CH_2-COOH$), 0.3 (1H, COOH)] spectra. Its mass spectrum exhibited an ion peak at *m/z* 271 (M+1), which established it as a cleavage product of I. Based on PMR signals and fragmentation pattern observed in the mass spectrum, the keto function could be located at various positions in the chain. The fragment ions due to α-cleavage of the carboxylic end were observed at *m/z* 101, 115, 129, 143, 157, 171, 185, 199, 213 and 227. In the light of the above observations, the product was characterized as a mono- keto derivatives of hexadecanoic acid. These findings based on α-cleavages due to keto function in the chain were in conformity with the results of Eck and coworkers[3].

The product IV displayed similar UV and IR (except band at 1715 cm^{-1} for isolated carbonyl) bands like the product II. The PMR spectrum was found to be very



Scheme 1

characteristic and indicated the isolated keto function in the chain by exhibiting a signal at δ2.3 integrating for four protons attributable to α-CH_2 to the keto group. Other signals were very much similar to those for II. The mass spectrum substantiated the formulation IV by giving a mass ion at m/z 325 (M + 1) as a monoketo derivatives of methyl 4-oxo-*trans*-2-octadecenoate (fragment ions due to α-cleavages of carboxylic end appeared at m/z 183, 197, 211, 225, 239 and 253). The position of ketonic function in the chain was again established by PMR and mass spectral data. Here again, our results based upon (α-cleavages due to keto group in respect of allylic keto function were similar to the earlier work[3].

A study of this allylic oxidation under various conditions showed that the yields of the co-product increased with longer reaction periods. Higher temperature (room temperature) was found favourable for the formation of III, but resulted in a lower yield of IV. However, in no case the absence of the co-products was observed. The yields of various monoketo derivatives, calculated on the basis of the intensity of α-cleavages to the isolated ketone group (given in experimental), were in good agreement with those positions conformationally favoured. These findings were further supported by similar results observed when the allylic oxidation of methyl *trans*-2-hexadecenoate and methyl *trans*-2-docosenoate, the lower and higher homologues of methyl *trans*-2-octadecenoate respectively, with chromium trioxide was carried out.

The mass spectra were recorded on a JEOL JMS-D300 instrument at 70 eV, PMR spectra on a Varian A60 instrument using TMS as internal standard, IR spectra on a Perkin-Elmer 621 spectrophotometer and UV spectra on a Perkin-Elmer 202 UV-visible spectrophotometer. Melting points were determined on a Kefler apparatus and are uncorrected.

The substrate, methyl *trans*-2-octadecenoate (I) was prepared from stearic acid according to the procedure of Palameta and Prostenik[5] and was characterized as reported earlier[6].

Reaction of I with chromium trioxide

The reagent was prepared by portionwise addition of chromium trioxide (5 g, 50 mmol) to a mixture of acetic anhydride (13 ml) and gl. acetic acid (25 ml) followed by dilution with benzene (25 ml) under ice-cooling. To this reagent solution compound I (2.96 g, 10 mmol) in benzene (5 ml) was added dropwise with stirring, and the temperature of reaction mixture maintained between 10 and 20 . TLC performed after 2 hr showed the formation of three products. All the three components responded positively to DNP test. The reaction mixture was diluted with water, neutralized with aq. NaOH, and extracted with ether. The etherial extract was dried (Na_2SO_4) and solvent removed *in vacuo* to give the product which was subjected to column chromatography over silica gel (60-120 mesh). Elution with pet. ether-ether (95 : 5) gave II in 75% yield, m.p. 68° (from hexane) (Found: C, 73.4; H, 10.0. $C_{19}H_{34}O_3$ requires C, 73.5; H, 10.0%; UV (methanol): 220 nm; IR (KBr): 1730 (ester CO), 1665 ($-CO-CH=CH-$), 1648 ($-CH=CH-$), 995 cm^{-1} (*trans*-unsaturation); PMR ($CDCl_3$): δ 7.05 (1H, *d*, J = 16 Hz, $-CO-CH=CH-COOCH_3$), 6.54 (1H, *d*, J = 16 Hz, $-CO-CH=CH-COOCH_3$), 3.79 (3H, *s*, $-COOCH_3$), 2.25 (2H, *t*, J = 7 Hz, $-CH_2-CO-CH=CH-$), 1.25 (24H, *br s*, chain CH_2), 0.9 (3H, *t*, terminal CH_3); MS: m/z 310 (M^+; 8%), 311 (M + 1; 12), 279 (M − OCH_3; 10); 278 (M − CH_3OH; 8), 251 (M − $COOCH_3$; 6), 169 (ε-cleavage between C-8 and C-9; 10), 155 (δ-cleavage between C-7 and C-8; 30), 141 (γ-cleavage between C-6 and C-7; 3), 137 (169 − CH_3OH; 18), 128 (McLafferty cleavage; 100), 123 (155 − CH_3OH; 16), 113 (α-cleavage between C-4 and C-5; 80), 97 (128 − OCH_3; 20), 96 (126 − CH_3OH; 28) and 85 [$(CH=CH-COOCH_3)^+$; 14].

Subsequent elution with pet. ether-ether (93 : 7) afforded III in 7% yield as a viscous liquid (Found: C, 71.1; H, 11.2. $C_{16}H_{30}O_3$ requires C, 71.1; H, 11.2%); IR (neat): 1715 (CO), 1705 cm^{-1} (carboxylic CO); PMR ($CDCl_3$): δ 2.28 (6H, *m*, $-CH_2-CO-CH_2$, CH_2COOH), 1.28 (20H, *br s*, chain CH_2), 0.9 (3H, *t*, terminal CH_3), −0.3 (1H, *br m*, COOH); MS: m/z 271 (M + 1; 1%), 253 (M − OH; 4), 225 (M − COOH; 4), 211 (M − CH_2COOH; 4), ions formed by α-cleavage of carboxylic end appeared at 101 (10), 115(15), 129(30), 143(10), 157(9), 171(11), 185(8), 199(5), 213(2.1), 227(1) and lower mass ions were: 102(2), 88(2), 87(14), 85(30), 73(78), 71(45), 57(75), 43(100).

Finally, elution with pet. ether-ether (90 : 10) provided IV in 16.8% yield, m.p. 55-62° (from hexane-methanol; 2 : 1) (Found: C, 70.3; H, 9.9. $C_{19}H_{32}O_4$ requires C, 70.3; H, 9.9%; UV (methanol): 220 nm; IR (nujol): 1735 (ester CO), 1715 ($CH_2-CO-CH_2-$), 1670 ($-CO-CH=CH-$), 1650 ($-CH=CH-$), 995 (*trans*-unsaturation); PMR ($CDCl_3$): δ 7.05 (1H, *d*, J = 16 Hz, $-CO-CH=CH-COOCH_3$), 6.55 (1H, *d*, J = 16 Hz, $-CH=CH-COOCH_3$), 3.79 (3H, *s*, $-COOCH_3$), 2.6 (2H, *t*, J = 7 Hz, $CH_2-CO-CH=CH-$), 2.3 (4H, *m*, $-CH_2-CO-CH_2$), 1.25 (18H, *br s*, chain $-CH_2$), 0.88 (3H, *t*, terminal CH_3); MS: m/z 325 (M + 1; 24%), 293 (M − OCH_3; 27), 265 (M − $COOCH_3$; 14), 239 (M − $CH=CHCOOCH_3$; 7), 211 (M − $COCH=CHCOOCH_3$; 7), 128 (McLafferty cleavage due to C_4-oxo; 12), 113 (α-cleavage between

C-4 and C-5; 77), 97 (128 $-OCH_3$; 27), 85 [$(CH=CH-COOCH_3)^+$; 51], ions formed by α-cleavages of carboxylic end appeared at 183(5), 197(8), 211(7), 225(6.4), 239(6.6), 253(4), and lower mass ions were: 85(51), 71(63), 57(80), 43(100).

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Phase-Transfer Catalyzed Oxidation of Benzylic Alcohols Involving Benzyltriethylammonium Chlorochromate†

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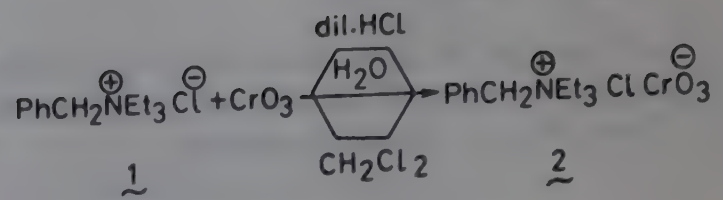
The product of reaction between chromium trioxide and benzyltriethylammonium chloride in dil. hydrochloric acid, water or dichloromethane is shown to be benzyltriethylammonium chlorochromate rather than a dichromate as reported earlier. The utility of this reagent in the oxidation of benzylic primary and secondary alcohols and cinnamyl alcohols in refluxing chloroform as well as under phase-transfer catalysis is described.

The oxidation of alcohols by Cr(VI) reagents under phase-transfer catalysis (PTC)[1-3] generally involves strongly acidic conditions incompatible with acid-sensitive substrates and unfavourable for selectivity. The recently reported solid-liquid PTC technique[4] using CrO_3 and some quaternary ammonium salts also lacks selectivity. We now report a PTC technique for the oxidation of benzylic primary and secondary alcohols under mild acidic conditions with a good potential for selectivity and with the advantages of economy, safety and large-scale applicability.

The product of addition of the quaternary ammonium salt **1** to CrO_3 in dil. HCl was earlier assigned a dichromate structure (**4**)[5] rather than the expected chlorochromate one (**2**). We found that this product (**2**) could be obtained either in an aq. medium or, more significantly, under neutral, non aq. conditions by the addition of CrO_3 to a CH_2Cl_2 solution of **1**. The presence of Cl in this product was easily demonstrated by the formation of AgCl in quantitative yield with aq. ethanolic $AgNO_3$ and also by a positive test for chromyl chloride. The same product could also be prepared by an exchange reaction between pyridinium chlorochromate (**3**) and **1** in water at 45° (Chart 1). These observations confirm that this product is indeed benzyltriethylammonium chlorochromate (**2**) rather than the dichromate (**4**).

The excellent selectivity[6] of this chlorochromate in the oxidation of benzylic and allylic alcohols in HMPT



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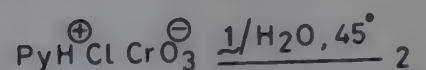

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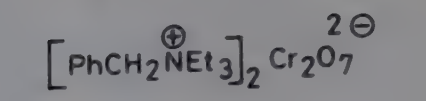

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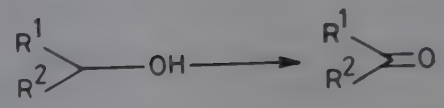

5 **6**

	R^1	R^2
a.	$CH_3(CH_2)_{16}$	H
b.	Ph CH_2 CH_2	CH_3
c.	$CH_3(CH_2)_6$	H
d.	Ph	H
e.	p-CH_3O C_6H_4	H
f.	m-CH_3O C_6H_4	H
g.	Ph	CH_3
h.	Ph CH=CH	H

at 60° has already been demonstrated[5]. Its utility, however, is limited by the high cost and toxicity of HMPT. Our results using this chlorochromate (**2**) generated *in situ* under phase-transfer conditions and also as a pre-formed reagent in refluxing chloroform in the oxidation of alcohols (**5**) (Chart 1) are presented in Table 1.

Inspite of the earlier misgivings[7] the present PTC procedure (*vide infra*) gave benzaldehydes or acetophenones (**6**) in fairly high yields. Saturated alcohols were relatively unreactive suggesting the possibility of selective oxidation. The presence of equimolar amount of NH_4Cl gave consistently better results than without it, and in the absence of the catalyst **1** the yields were lowered by about 25% with incomplete conversions. The excellent yield of *p*-methoxybenzaldehyde from the acid-sensitive *p*-methoxybenzyl alcohol is worth noting.

A significant outcome of this work is the considerable difference in reactivity between the

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Table 1 – Oxidation of Alcohols (**5**) with Benzyltriethylammonium Chlorochromate by PTC Procedure

Compd	Yield[a] (%)	Reaction period (hr)	Temperature (°C)	IR (CCl_4) $\nu C=O$ (cm^{-1})
6a	—	24	25	—
6b	15[b]	24	25	1710
6c	30[b](–)	24	25	1725
6d	72(77)	20	20	1700
6e	75	20	25	1690
6f	75	24	25	1700
6g	50[b,c](77)	24	20	1688
6h	45[d](78)	20	25	1682

(a) Isolated yield of the product. Values in parentheses refer to isolated yields in refluxing chloroform (6 hr reflux) using 1.5 equiv of the reagent **2**.
(b) Estimated yields by PMR analysis.
(c) Yield could be increased to 75% (isolated) by carrying out the reaction in the presence of one molar equiv of acetic acid.
(d) Yield increased to 65% using 2.5 molar equiv of chromium trioxide in the presence of equimolar sodium acetate. Yield of benzaldehyde, isolated by fractional distillation, was 11%.

secondary alcohol **5g** and the primary benzyl alcohols. Such a difference in Cr(VI) oxidations does not seem to have been commented upon in recent work involving chlorochromates and dichromates. The yield of the acetophenone **6g** could, however, be increased from 50% (estimated) to 75% (isolated) by the addition of an equimolar amount of acetic acid to the reaction mixture. Addition of acetic acid had no significant effect on the oxidation of other alcohols. The difference in reactivity, noted above between **5 g** and other benzyl alcohols, was lost in refluxing chloroform using 1.5 equiv of the reagent **2**.

Cinnamyl alcohol underwent considerable degradation to benzaldehyde in the PTC procedure while it could be smoothly oxidized to cinnamaldehyde with 1.5 equiv of **2** in refluxing chloroform. Cleavage to benzaldehyde could, however, be suppressed to about 10% and the yield of cinnamaldehyde increased from 45 to 65% using 2.5 equiv of CrO_3 in the presence of 2.5 equiv of NaOAc as a buffering agent. Cinnamaldehyde and cinnamyl acetate remained unaffected under the experimental conditions showing that it is cinnamyl alcohol which undergoes cleavage. Similar cleavage of cinnamyl alcohol has been reported earlier during Cr(VI) oxidations[3-8].

Benzyltriethylammonium chlorochromate (**2**)

Method (*a*) – A solution of CrO_3 (25 g, 0.25 mol) in water (50 ml) was added in a thin stream to a stirred solution of **1** (56.87 g, 0.25 mol) in water (150 ml) at 15 After stirring for 1 hr at 15°, the orange solid was filtered, washed with cold water, recrystallized from aq. acetone and dried in a vacuum oven to give **2**, m.p. 88-89 , yield 60 g (73%); IR (nujol): 950, 925, 905, 885, 760, 710, 440 cm^{-1}; PMR ($CDCl_3$): 1.40 (*t*, 9H, $3\times CH_2-CH_3$), 3.30 (*q*, 6H, $3\times CH_2CH_3$), 4.50 (*s*, 2H, $Ph-CH_2$) and 7.36 (*s*, 5H, $Ar-H$) (Found: C, 47.3; H, 6.5; N, 4.5; Cl, 10.6; Cr, 16.1. $C_{13}H_{22}ClCrNO_3$ requires C, 47.6; H, 6.7; N, 4.3; Cl, 10.8; Cr, 15.9%).

Method (*b*) – Powdered CrO_3 (10 g, 0.1 mol) was added in portions to a stirred solution of **1** (22.75 g, 0.1 mol) in CH_2Cl_2 (300 ml) and stirring continued for 1 hr. Removal of solvent under reduced pressure gave a brown crystalline solid (29.25 g), m.p. 85-86° which on recrystallisation from aq. acetone gave **2** (24 g, 73%), m.p. 86-88°, identical in all respects with that obtained from method (a).

Method (*c*) – Chromium trioxide (5 g, 0.05 mol) was added to 6*N* HCl (8.4 ml) at 0-5° followed by pyridine (3.71 ml). The mixture was stirred for 30 min. The precipitated pyridinium chlorochromate was redissolved by warming to 40-45° and a solution of **1** (22.75 g, 0.1 mol) in water (13 ml) added slowly to it. After stirring for 30 min at 40-45°, the reaction mixture was diluted with water (13 ml) and cooled to 5°. The resultant orange solid was filtered, washed with water and dried to give **2**, m.p. 87-90°, 15.6 g (95%) identical in all respects with that obtained from method (a).

PTC procedure for the oxidation of alcohols (**5**):
General procedure

To a solution of CrO_3 (15 g, 0.15 mol) in water (20 ml) at 25° was added a solution of NH_4Cl (8.03 g, 0.15 mol) in water (20 ml) followed by **1** (3.41 g, 0.015 mol) and CH_2Cl_2 (50 ml). A 10% solution of the alcohol (**5**; 0.1 mol) in CH_2Cl_2 was added slowly during 30 min, maintaining the temperature at 25°. The reaction mixture was then stirred for 24 hr at 25-30°, diluted with ether and insoluble Cr salts were filtered off. The organic layer was washed with 2% aq. NaOH solution, water and brine and passed through a short column of alumina. After removal of solvent the residue was distilled in a Kugelrohr apparatus and characterized by its IR and PMR spectra and by conversion into 2,4-dinitrophenylhydrazone derivative.

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Quinolinium Dichromate—A New Reagent for Oxidation of Alcohols

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Quinolinium dichromate is shown to be a new oxidising agent for the selective oxidation of primary and secondary alcohols to aldehydes and ketones respectively.

Primary and secondary alcohols have been oxidised by a variety of Cr(VI) reagents[1,2], such as pyridine-chromium trioxide complexes[3], pyridinium chlorochromate[4], pyridinium dichromate[5], 2,2′-bipyridinium chlorochromate[6], etc. We have been interested in the selective oxidation of primary and secondary alcoholic groups present in the amino acid residues of collagen. Due to poor solubility of Cr(VI) reagents reported prior to pyridinium chlorochromate in water, these reagents were not useful for collagen. However, our efforts in this direction were successful with pyridinium chlorochromate[7,8]. This note reports the preparation of quinolinium dichromate (QDC)[9], $(C_9H_7NH^+)_2Cr_2O_7^{2-}$ and its application in the oxidation of alcohols.

Quinolinium dichromate, a stable orange solid, m.p./160-61°, was prepared by dissolving CrO_3 in water, adding quinoline and collecting the product. The structure of the product was confirmed by elemental analyses and the infrared spectrum (KBr) which exhibited bands at 930, 875, 765 and 730 cm^{-1}, characteristic of the dichromate ion[10].

QDC is soluble in water, dimethylformamide and dimethyl sulphoxide, sparingly soluble in methylene chloride and chloroform, and insoluble in heptane, toluene, ether and ethyl acetate. We have carried out the oxidation experiments with solutions of QDC in dimethylformamide or suspensions in methylene chloride.

QDC (1 molar equiv.) oxidises primary alcohols to the corresponding aldehydes in refluxing CH_2Cl_2 (4 hr) and reasonably oxidises secondary alcohols to ketones. Solutions of QDC (1.5 molar equiv.) in DMF oxidise both saturated and allylic alcohols to the corresponding aldehydes at 30°. Under the same conditions, crotonaldehyde, cinnamaldehyde and benzaldehyde furnish the corresponding acids. The details of the oxidation by QDC in CH_2Cl_2 and DMF are given in Table 1.

This reagent works as efficiently as activated manganese dioxide[11] or Collins' reagent[3].

Pyridinium dichromate in DMF is reported[5] to convert primary alcohols to the corresponding acids, in contrast to the exclusive formation of aldehydes by QDC in DMF. We have also prepared quinolinium chlorochromate and its efficacy as an oxidising agent is under investigation.

Quinolinium dichromate

To a stirred solution of CrO_3 (100 g) in water (100 ml) cooled in ice, quinoline (86 ml) was added in small portions. The solution was diluted with acetone (400 ml), cooled to −20° and the orange solid which separated out was filtered, washed with acetone, dried *in vacuo* and re-crystallized from water; m.p. 160-61°; yield (72%) Found: C, 45.1; H, 3.2; N, 5.6. Calc. for $C_{18}H_{16}N_2Cr_2O_7$: C, 45.4; H, 3.4; N, 5.9%).

Table 1—Oxidation of Alcohols by QDC in CH_2Cl_2 and DMF

Compd	Product	Yield (%)* (QDC in CH_2Cl_2)	b.p. (°C)	Lit b.p. (°C)
n-Butanol	*n*-Butanal	69(74)	74.5	75
n-Hexanol	*n*-Hexanal	70(44)	130	131
Benzyl alcohol	Benzaldehyde	45(45.4)	177.5	179
Cinnamyl alcohol	Cinnamaldehyde	70(52.3)	251	252
Benzhydrol	Benzophenone	55(48)	48.5†	49†
Benzaldehyde	Benzoic acid	(55.3)	121.5†	122*
Cinnamaldehyde	Cinnamic acid	(52.3)	132†	133†
Crotonaldehyde	Crotonic acid	(85)	71.5†	72†

*Values in parenthess refer to yields in DMF as a reaction medium.
†Melting point.

Typical oxidation procedure: Oxidation of n-butanol in (i) methylene chloride

To a stirred solution of quinolinium dichromate (23.8 g) in CH_2Cl_2 (48 ml) was added dropwise a solution of *n*-butanol (3.7 ml) in CH_2Cl_2 (7 ml). The mixture was refluxed for 4 hr, cooled to room temperature, diluted with ether and filtered through a small amount of silica gel. The solvent was evaporated and the product distilled.

(ii) DMF

In the case of DMF as solvent similar conditions were adopted, except after stirring for 4 hr, the mixture was poured into excess of water and extracted with ether.

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Reactions of Nitrophenols with Phosphorus Oxychloride in Dimethylformamide

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A rapid and simple method for the replacement of hydroxyl group of nitrophenols and related compounds by chlorine using phosphorus oxychloride in dimethylformamide at ambient temperature is described.

A couple of reagents, with $POCl_3$ as the common ingredient are available in old literature[1,2] for the replacement of phenolic hydroxyl by chlorine in nitrophenols. We have presently observed that a mixture of $POCl_3$ and DMF constitutes an effective reagent for this purpose at ambient temperature. The method is simple and rapid and provides the chloro derivatives in good yields (60-90%).

Thus 4-nitro-, 2,6-dinitro-, 2,4-dinitro-, 2,5-dinitro-, 3,4-dinitro-, 2,4,5-trinitro- and 2,4,6-trinitro-phenols could be converted into the corresponding chlorobenzenes, identified by direct comparison with authentic samples. Similarly 2-hydroxy-3,5-dinitrobenzoic acid, 4-hydroxy-3,5-dinitrobenzaldehyde, 4-hydroxy-3-nitrocoumarin and 4-hydroxy-6-methyl-3-nitro-2*H*-pyran-2-one were converted into the corresponding chloro derivatives in 90, 85, 70 and 60% yields respectively, the identity of the chloro derivatives being confirmed by direct comparison with authentic samples. Thus this method is of general applicability.

Procedure

The appropriate nitrophenol (0.008 mol) was gradually introduced with stirring to a mixture of $POCl_3$-DMF (1:1, 8 ml). After 2 hr at room temperature, the reaction mixture was poured into ice-water to obtain the chloro derivatives as the solids.

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Stereochemical Studies by PMR Spectroscopy: Methoxybromination of the Olefinic Bond in Bicyclic Systems

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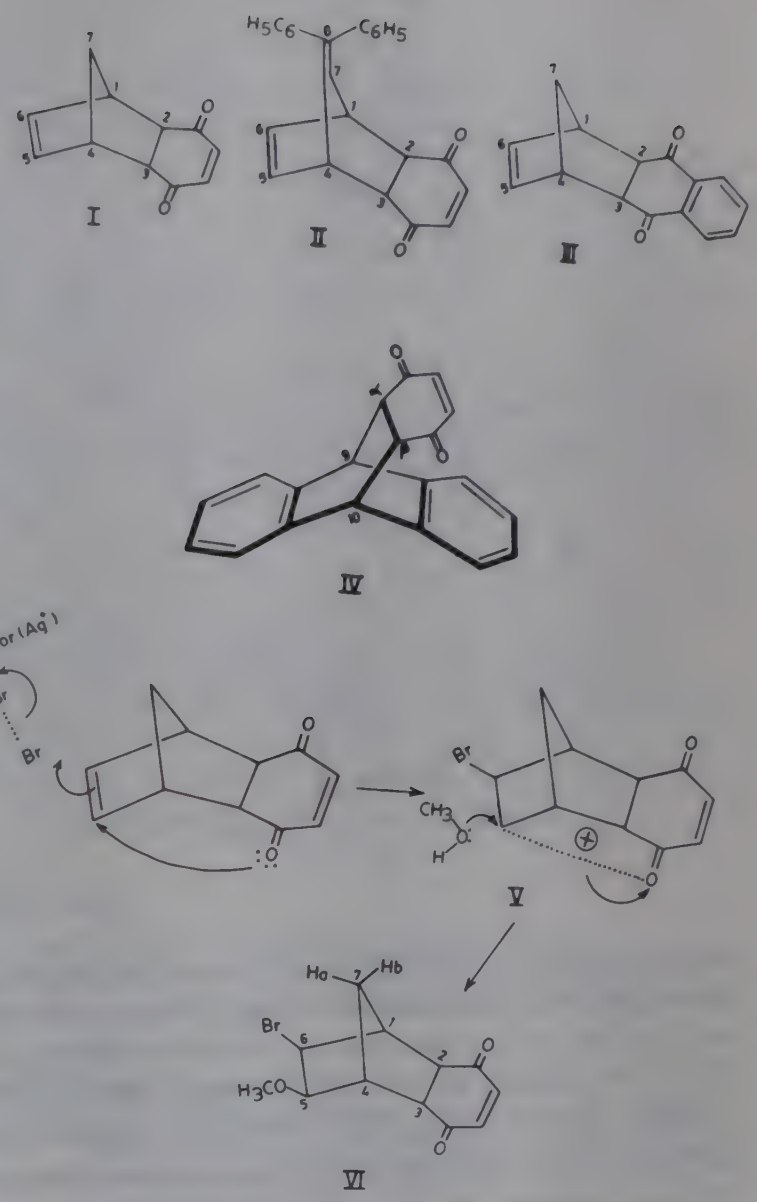
Received 21 *February* 1985; *revised and accepted* 25 *July* 1985

Methoxybromination of the olefinic bond in some typical Diels-Alder adducts with bromine in methanol in the presence of yellow lead oxide or silver nitrate has been effected. The assignment of stereochemistry of the methoxybromo products has been made with the help of PMR spectroscopy. Cyclopentadiene-*p*-benzoquinone, 6,6-diphenylfluvene-*p*-benzoquinone and cyclopentadiene-1,4-naphthoquinone Diels-Alder adducts (I-III) undergo *exo-cis*-addition while anthracene-*p*-benzoquinone adduct (IV) leads to the formation of *trans*-product. The bromine atom and the methoxy group of the methoxybromo adduct of IV are present in *trans*-1,2-diaxial positions in the cyclohexadione ring having chair type conformation.

Methoxybromination of the olefinic bond has been quite interesting[1,2]. The *trans*-addition of methyl hypobromite to the various alkenes has been established by spectral and chemical studies[3,4]. The strained olefinic systems behave differently and have been found to undergo *cis*-electrophilic addition. However, the olefinic bicyclic systems undergo *exo-cis*- and *trans*-additions[1-5] of bromine. It was therefore considered of interest to investigate the addition of bromine in methanol to the olefinic bond in bicyclic systems. We report herein the methoxybromination of the olefinic bond in cyclopentadiene-*p*-benzoquinone (I), 6,6-diphenylfulvene-*p*-benzoquinone (II), cyclopentadiene-1,4-naphthoquinone (III), and anthracene-*p*-benzoquinone (IV) Diels-Alder adducts with bromine in methanol in the presence of a trapping agent (silver nitrate or yellow lead oxide) and stereochemical assignment of the addition products with the help of PMR spectroscopy.

The PMR spectra of the methoxybrominated cyclopentadiene-*p*-benzoquinone *endo*-adduct (VI) and cyclopentadiene-1,4-naphthoquinone *endo*-adduct (VIII) displayed two doublets ($J = 7$ Hz) due to C-5 and C-6 methine protons. However, the PMR spectrum of 6,6-diphenylfulvene-*p*-benzoquinone *endo*-adduct methoxybromide (IX) exhibited the methine protons ($-CH$Br and $-CH$OCH$_3$) as two doublets ($J = 6.8$ Hz) each of 1H intensity along with signals for other protons (*vide infra*). Based on coupling constant Anet[8] investigated the stereochemistry of bornane-2,3-diol. The coupling constants 7.7 and 8.9 Hz were assigned for *cis-exo-exo*- and *cis-endo-endo*-diols respectively, whereas 2.2 Hz was attributed for *trans*-diol. The coupling constant of the doublet for C-5 and C-6 methine protons was of a similar order as that reported for the *exo-cis*-configuration of bornane-2,3-diol, and supported the *exo-cis*-geometry for the bromine atom and the methoxy group. The absence of C-4 and C-5 coupling of methine protons further demonstrated that the methoxy group occupies and *exo*-position in consistence with Anet's[8] observation. A large internal chemical shift of the methylene *AB* quartet suggested that the addition of bromine atom occurs from the methylene bridge side and, therefore the *exo-cis*-geometry for the bromine atom and the methoxy group was assigned. The possibility for the formation of a *trans*-product was eliminated, since for such product one would expect the coupling constant of ~2 Hz for C-5 and C-6 methine protons. The appearance of methoxy protons at 3.28 in VIII further



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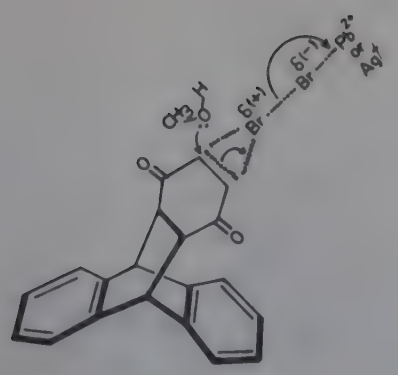

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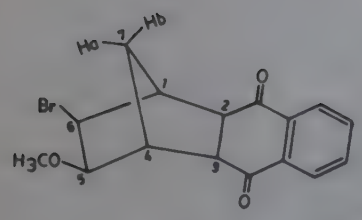
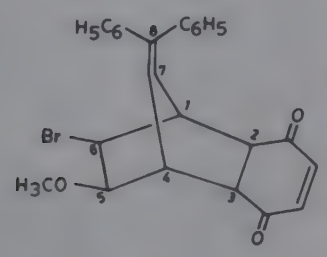
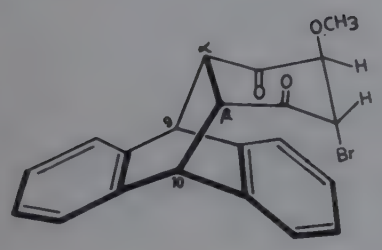


VIII



IX



X

demonstrated its *exo*-orientation because in the case of *endo*-orientation it would have been influenced by the benzene ring of the cage-moiety. The olefinic bridge (C-7) in the adduct II did not undergo electrophilic addition due to steric effect. Molecular models also supported the *exo-cis*-geometry of bromine atom and methoxy group in IX, the methoxybromination product of II.

Electrophilic addition to the olefinic bond between C-5 and C-6 will be considered more facile as compared with the addition to the olefinic bond of the dienophile moiety. The π-electron density of the olefinic bond of the dienophile moiety is diluted by the resonance due to adjacent carbonyl groups and hence the developing carbonium ion will be destabilized.

The PMR spectrum of the compound X exhibited two doublets ($J = 2.5$ Hz) each of 1H intensity for the $-CHBr$ and $-CHOCH_3$ methine protons and two multiplets each of 1H intensity for C-9 and C-10 methine protons along with resonances for other protons (*vide infra*). The absence of any olefinic signal (~ 6.5) in the spectrum of X indicated that the electrophilic addition took place on the double bond. The coupling constant ($J = 2.5$ Hz) which arises due to the diequatorial interaction of methine protons, would favour the chair type conformation for the cyclohexadione ring in X. This provided a strong evidence for X to be the *trans*-1,2-diaxial addition product. The appearance of methoxy protons at the normal position (~ 3.30) suggested that the addition of methoxy group occurred from the opposite side of the cage-benzo ring. The deshielding of the C-10 methine proton is expected due to twisting of one of the carbonyl groups as the C-9 and C-10 protons are magnetically non-equivalent. Molecular models also supported the structure X. The *trans*-diaxial[9] orientation was further supported by IR studies. Jones *et al.*[10] have suggested that if bromine enters at an equatorial position adjacent to the carbonyl of cyclohexenone ring in the chair conformation, the carbonyl stretching frequency is enhanced by 20 cm^{-1} while in axial position the carbonyl stretching remain unchanged[11,12]. A strong absorption at 1725 cm^{-1} due to the carbonyl groups in X supported the 1,2-diaxial orientation of the bromine atom and methoxy group as this absorption correspond to a normal cyclohexanone system.

The *exo-cis*-addition of methyl hypobromite (CH_3OBr) to the olefinic bond of the bicyclic *endo*-adducts (I-III) has been explained in terms of an interaction of the carbonyl group (*endo*) and the olefinic double bond (C-5) via an intermediate V, while the *trans*-addition in IV proceeds through the ion pair intermediate VII.

PMR spectra were recorded in $CDCl_3$ on a Varian A-60D spectrometer at 45° using TMS as internal standard (chemical shifts in δ, ppm), and IR spectra in nujol mull on a Perkin-Elmer 720 spectrophotometer. The characterization data of various compounds prepared are given in Table 1.

Cyclopentadiene-p-benzoquinone (*endo*) *Diels-Adducts* (*I*)

It was prepared according to the method of Diels and Alder[13] by stirring freshly distilled cyclopentadiene with *p*-benzoquinone in equimolar proportions in dry benzene at 0-10° for 6 hr. The solvent was removed under reduced pressure and the product recrystallised from petroleum-ether; PMR: 1.53 (*q*, 2H,

Table 1—Physical Data of the Adducts (I-IV) and Their Methoxybromo Products (VI and VIII-X)

Compd	m.p. °C	Mol. formula	Found (%) (Calc.)	
			C	H
I	66-67	$C_{11}H_{10}O_2$	75.5 (75.8)	5.8 (5.8)
II	98-99	$C_{24}H_{18}O_2$	85.1 (85.2)	5.4 (5.3)
III	90-92	$C_{15}H_{12}O_2$	80.0 (80.4)	5.5 (5.4)
IV	211-13	$C_{20}H_{14}O_2$	84.1 (83.9)	5.0 (4.9)
VI	90-92	$C_{12}H_{13}O_3Br$	50.2 (50.5)	4.6 (4.6)
VIII	110-12	$C_{16}H_{15}O_3Br$	56.9 (57.3)	4.6 (4.5)
IX	108-10	$C_{25}H_{23}O_3Br$	66.3 (66.5)	5.2 (5.1)
X	160-62	$C_{21}H_{17}O_3Br$	63.3 (63.5)	4.4 (4.3)

7-CH_2), 3.20 (*t*, 2H, C_2-H and C_3-H), 3.60 (*m*, 2H, C_1-H and C_4-H), 6.16 (*t*, 2H, C_5-H and C_6-H) and 6.65 (*s*, 2H, olefinic protons of the dienophile moiety). dienophile moiety).

6,6-*Diphenylfulvene-p-benzoquinone* (*endo*) *Diels-Alder adduct* (*II*)

Equimolecular amounts of 6,6-diphenylfulvene and *p*-benzoquinone in dry benzene were refluxed for abour 90 min, benzene removed under reduced pressure and the product recrystallised from ethanol; PMR: 3.62 (*m*, 2H, C_2-H and C_3-H), 3.97 (*m*, 2H, C_1-H and C_4-H), 6.32 (*t*, 2H, C_5-H and C_6-H), 6.64 (*s*, 2H, olefinic protons of the dienophile moiety) and 7.24 (*m*, 10H, Ar-*H*).

Cyclopentadiene-1,4-*naphthoquinone* (*endo*) *adduct* (*III*)

It was prepared by stirring freshly distilled cyclopentadiene (monomer) with 1,4-naphthoquinone in equimolecular proportions in dry benzene at room temperature for 12 hr. Benzene was removed under reduced pressure and the product recrystallized from ethanol; PMR: 1.58 (*bs*, 2H, 7-CH_2), 3.51-3.68 (*m*, 4H, C_1-H, C_3-H and C_4-H), 6.06 (*t*, 2H, C_5-H and C_6-H) and 7.65 (*m*, 4H, Ar-*H*).

4nthrancene-p-benzoquinone adduct (*IV*)

It was prepared according to the method of Diels and Alder[14]. Anthracene (5.65 g) and *p*-benzoquinone (3.60 g) were refluxed in xylene (35 ml) for about 50 min. On cooling, the solid was collected, thoroughly washed with hot water and recrystallized from xylene; PMR; 3.75 (*t*, 2H, α-H and β-H), 4.92 (*t*, 2H, C_9-H and C_{10}-H), 6.32 (*s*, 2H, olefinic protons) and 7.30 (*m*, 8H, Ar-*H*).

Methoxybromination of the adducts (*I, II, III and IV*)

A solution of bromine (0.03 mol) in methanol (75 ml) was added to a stirred suspension of the adduct (0.025 mol) in methanol (150 ml) containing silver nitrate (0.03 mol) or yellow lead oxide (0.02 mol) at room temperature. The reaction mixture was further stirred for about 16 hr and precipitated silver or lead bromide filtered off. Methanol was removed from the filtrate, the residue treated with ether and the insoluble inorganic material filtered off. The ethereal solution was treated with saturated sodium bicarbonate solution to neutralize nitric acid produced in reaction when $AgNO_3$ was used as the trapping agent. The ethereal extract was then washed with water, dried (anhyd. Na_2SO_4) and solvent removed to give the methoxybromination product (VI, VIII, IX or X), which recrystallized from ethanol. The PMR data of the products are given below:

VI: 2.45, 1.97 (AB_q, 2H, J = 10 Hz, 7-CH_2), 3.12 (*m*, 2H, C_2-H and C_3-H), 3.28 (*s*, 3H, $-OCH_3$), 3.76 (*m*, 2H, C_1-H and C_4-H), 4.14 (*d*, 1H, J = 7 Hz, C_6-H), 4.86 (*d*, 1H, J = 7 Hz, C_5-H) and 6.67 (*s*, 2H, olefinic protons).

VIII: 2.48, 2.00 (AB_q, 2H, J = 10 Hz, 7-CH_2), 3.28 (*s*, 3H, $-OCH_3$), 3.31 (*m*, 2H, C_2-H and C_3-H), 3.50 (*m*, 2H, C_1-H and C_4-H), 4.19 (*d*, 1H, J = 7 Hz, C_6-H), 4.82 (*d*, 1H, J = 7 Hz, C_5-H) and 7.32 (*m*, 4H, Ar-*H*).

IX: 3.30 (*s*, 3H, $-OCH_3$), 3.56 (*m*, 2H, C_2-H and C_3-H), 3.67 (*m*, 2H, C_1-H and C_4-H), 4.25 (*d*, 1H, J = 6.8 Hz, C_6-H), 4.90 (*d*, 1H, J = 6.8 Hz, C_5-H), 6.61 (*s*, 2H, olefinic protons) and 7.32 (*m*, 10H, Ar-*H*).

X: 3.31 (*s*, 3H, $-OCH_3$), 3.47 (*m*, 2H, α-H and β-H), 4.18 (*d*, 1H, J = 2.5 Hz, $-CHBr$), 4.96 (*d*, 1H, J = 2.5 Hz, $-CHOCH_3$), 4.89 (*m*, 1H, C_9-H), 5.01 (*m*, 1H, C_{10}-H) and 7.23 (*m*, 8H, Ar-*H*).

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Studies on Coumarin Derivatives: Part III† —Synthesis & Biological Activity of Some 2-[Aryl/heteroaryl-carbonyl-methylthio]-6-methyl-8H-pyrano[2,3-*e*] benzoxazol-8-one

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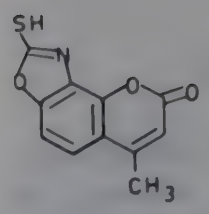
8-Amino-7-hydroxy-4-methylcoumarin on treatment with carbon disulphide in alkaline medium gives 2-mercapto-6-methyl-8H-pyrano[2,3-*e*]benzoxazol-8-one (I). The reaction of I with various phenacyl bromides and 3-(ω-bromoacetyl)coumarins gives the title compounds (II and III).

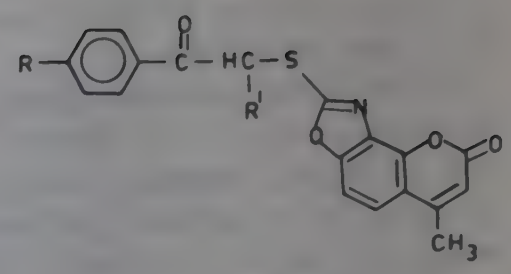
Coumarin derivatives form an important group of naturally occurring compounds displaying diverse biological activities[1,2]. The isolation of oxazolo[3,4-*d*]coumarin from the broad spectrum antibiotic Novobiocin[3] and the syntheses of 6H-pyrano[3,2-*f*]benzoxazol-6-ones[4], and 8H-pyrano[3,2-*e*]benzoxazol-8-ones[5] prompted us to synthesize the title compounds as analogues of this antibiotic. Moreover, number of 2-substituted mercapto-oxazoles[6] have been found to exhibit appreciable insecticidal and tuberculostatic activities. In view of this and our continuing interest in the synthesis of heterocyclic compounds from coumarin derivatives[7], we report herein the synthesis and biological activity of title compounds (II and III).

The starting compound 2-mercapto-6-methyl-8H-pyrano[2,3-*e*]benzoxazol-8-one (I) was prepared by the interaction of 8-amino-7-hydroxy-4-methylcoumarin with carbon disulphide in the presence of methanolic KOH. The structure of the compound I was established on the basis of elemental analyses and IR data.

Compound (I) on reaction with phenacyl bromides and substituted 3-(ω-bromoacetyl)coumarins[8] either (i) in ethanolic KOH or (ii) in a mixture of anhydrous ethanol and DMF furnished II and III. The products resulted by these two methods were identical (m.m.p., and co-TLC). However, method (ii) gave the products



I



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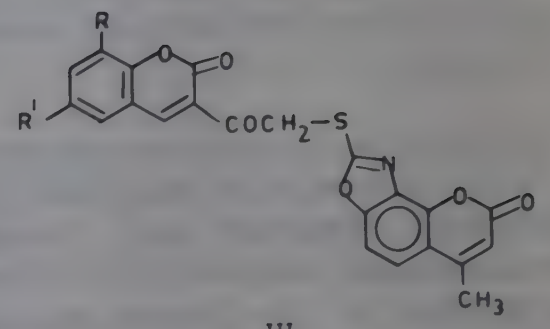

III

in much better yields. The structures of II and III were supported by their IR, PMR and mass spectra. The IR and PMR data for the representative compounds IIa and IIIa are only given.

Biological activity

All the compounds were tested for their antibacterial[9] (against *Esch. coli* and *Bacillus magaterium*) and antifungal[10] (against *Curvularia lunata* and *Dreschlera halodes*) activities at the concentration of 400-600 μg/ml. None of the compounds showed any noteworthy activity.

All the melting points were determined in open capillaries using sulphuric acid bath and are uncorrected.

2-Mercapto-6-methyl-8H-pyrano[2,3-e]benzoxazol-8-one (I)

A mixture of 8-amino-7-hydroxy-4-methylcoumarin (0.01 mol), carbon disulphide (10 ml), KOH (0.02 mol), methyl alcohol (40 ml) and water (10 ml) a°no[*2,3-e*]*benzoxazol-8-one (I)*

A mixture of 8-amino-7-hydroxy-4-methylcoumarin (0.01 mol), carbon disulphide (10 ml), KOH (0.02 mol), methyl alcohol (40 ml) and water (10 ml) was refluxed for 24 hr, cooled and acidified. The precipitate was filtered and recrystallised from aq. ethanol to give I, m.p. 275°.

2-[(*Aryl-carbonyl-methylthio*]-6-*methyl*-8*H*-*pyrano*[2,3-*e*]*benzoxazol*-8-*one* (*II*)

(i) Compound (I; 0.01 mol) in ethanol containing

†For Parts I and II of the series, see ref. 7.

Table 1—Characterization Data of II and III

Compd*	R	R′	m.p. (°C)	Mol. formula	Cryst. form.	N† (%)		S (%)	
						Found	Calc.	Found	Calc.
IIa	H	H	178	$C_{19}H_{13}NO_4S$	Methanol	3.96	3.98	9.10	9.11
IIb	NO_2	H	190	$C_{19}H_{12}N_2O_6S$	Methanol	7.04	7.07	8.08	8.08
IIc	Cl	H	202	$C_{19}H_{12}NO_4ClS$	Methanol	3.60	3.63	8.30	8.31
IId	OCH_3	H	227	$C_{20}H_{15}NO_5S$	Chloroform	3.60	3.67	8.37	8.39
IIe	CH_3	H	222	$C_{20}H_{15}NO_4S$	Chloroform	3.80	3.83	8.72	8.76
IIf	H	Ph	238	$C_{25}H_{17}NO_4S$	Chloroform	3.26	3.27	7.48	7.49
IIIb	OCH_3	H	294	$C_{23}H_{15}NO_7S$	Dioxan-Pet.ether	3.00	3.11	7.10	7.12
IIIc	H	Cl	260(d)	$C_{22}H_{12}NO_6ClS$	DMF + EtOH	3.06	3.09	7.04	7.06
IIId	NO_2	H	261	$C_{22}H_{12}N_2O_8S$	Dioxan-Pet.ether	6.00	6.03	6.88	6.89
IIIe	H	Br	178	$C_{22}H_{12}NO_6BrS$	DMSO	2.80	2.81	6.40	6.42
IIIf	Br	Br	270	$C_{22}H_{11}NO_6Br_2S$	DMSO	2.40	2.42	5.52	5.54

*Compounds were obtained in 50-60% yields
†Satisfactory C, H analyses were obtained.

few flakes of KOH (0.01 mol) was warmed until it dissolved. To this was added appropriate phenacyl bromide (0.01 mol), refluxed for 8 hr, cooled, the solid separated filtered off, washed with water and crystallised from suitable solvents, yield 40-45% (Table 1).

(ii) A mixture of I (0.01 mol) and phenacyl bromide (0.01 mol) in a mixture of anhydrous ethanol (15 ml) and DMF (15 ml) was refluxed for 5 hr. The reaction mixture was cooled, the solid separated was filtered, washed thoroughly with water and crystallised from suitable solvents, yield 50-60%. IIa: IR (nujol, ν_{max} cm $^{-1}$): 1175, 1375 and 1595 (absorption bands of heterocyclic oxazole ring system), 1675 (−C=O), and 1720 (lactone −C=O); PMR ($CDCl_3$): δ 2.45 (*s*, 3H, $-CH_3$), 5.05 (*s*, 2H, $-CH_2-$), 6.20 (*s*, 1H, C−7H) and 7.20-7.65 (*m*, 7H, Ar-H); MS: *m/z* 351 (60%), 319 (M^+-S, 14%), 305 (40%), 233 (5%), 232 (10%), 204 (10%), 202 (12%), 105 (100%) and 77 (28%).

2-[(2-*Oxo*-2*H*-1-*benzopyran*-3-*yl*)*carbonylmethyl-thio*]-6-*methyl*-8*H*-*pyrano*[2,3-*e*]*benzoxazol*-8-*one* (*IIIa*; *R*, *R′* = *H*)

(i) I (2.33 g, 0.01 mol) in ethanol containing KOH (0.01 mol) was warmed until the I dissolved. To this was added 3-(ω-bromoacetyl)coumarin (2.67 g, 0.01 mol) and the reaction mixture refluxed for 8 hr, cooled, the solid separated filtered, washed with water and crystallised from DMSO to yield IIIa, m.p. 278°; yield 40%.

(ii) II (2.33 g, 0.01 mol) and 3-(ω-bromoacetyl)coumarin (2.67 g, 0.01 mol) in anhydrous ethanol and DMF (each 15 ml) were refluxed for 5 hr, cooled when a solid separated out which was washed with water and crystallised from DMSO; m.p. 278°, yield 60% (Found: C, 63.1; H, 3.0; N, 3.3; S, 7.6. $C_{22}H_{13}NO_6S$ requires C, 63.0; H, 3.1; N, 3.3; S, 7.6%); IR (KBr, ν_{max} cm $^{-1}$): 1175, 1365 and 1595 (vibrations arising from heterocyclic oxazol system), 1660 (C−C=O) and 1720-1740 (ω-type band for lactone carbonyls of two coumarin rings); PMR (DMSO-d_6): δ 2.40 (*s*, 3H, $-CH_3$), 5.00 (*s*, 2H, $-CH_2-$), 6.10 (*s*, 1H, coumarin C-3 proton), 7.1-7.52 (*m*, 6H, aromatic protons) and 8.80 (*s*, 1H, C4′-H of coumarin).

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Synthesis of 2-Aroyl-3-methyl-7-phenyl-5*H*-furo[3,2-*g*][1]benzopyran-5-ones as Possible Anti-implantation Agents

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2-Aroyl-3-methyl-7-phenyl-5*H*-furo[3,2-*g*][1]benzopyran-5-ones (Va-e) have been prepared by the cyclization of 2-aroyl-5-benzoylacetyl-6-hydroxy-3-methylbenzofurans (IVa-e) with acetic acid and conc. sulphuric acid. 2-[4-(*β*-*t*-Alkylaminoalkyloxy)benzoyl]-3-methyl-7-phenyl-5*H*-furo[3,2-*g*][1]benzopyran-5-ones (VIa-d) have also been prepared. None of the compounds shows any antifertility activity.

6,4′-Dihydroxyflavone[1], quercetin[2], rubinin[3], 2-aroyl-3-ethylbenzofurans[4], chromones[5], and isoflavones[6] have been shown to exhibit marked estrogenic activity. We envisaged that incorporation of aroylbenzofuran and 2-phenylbenzopyrone moieties in a rigid cyclic system such as linear aroylfuranoflavones may enhance their anti-implantation activity. In order to realise our objective, herein we report the synthesis and anti-implantation activity of linear furanobenzopyrones (Va-f and VIa-d).

The starting 5-acetyl-2-aroyl-6-hydroxy-3-methylbenzofurans (IIIa-e) were synthesised in 75-80% yield by the condensation of resdiacetophenone (I) with different *p*-substituted phenacyl bromides[7] (IIa-e). Compounds (IIIa-e) on treatment with benzoyl chloride in acetone-potassium carbonate gave the intermediate diaroylmethanes[8] (IVa-e) which on heating with acetic acid and conc sulphuric acid underwent cyclization to yield the required aroylbenzopyranones[9] (Va-e, Chart 1).

Many furanocoumarins[10,11] and benzofurans[12] having alkylaminoalkoxy substitution exhibit antifertility activity. Hence [*p*-(*t*-alkylamino-

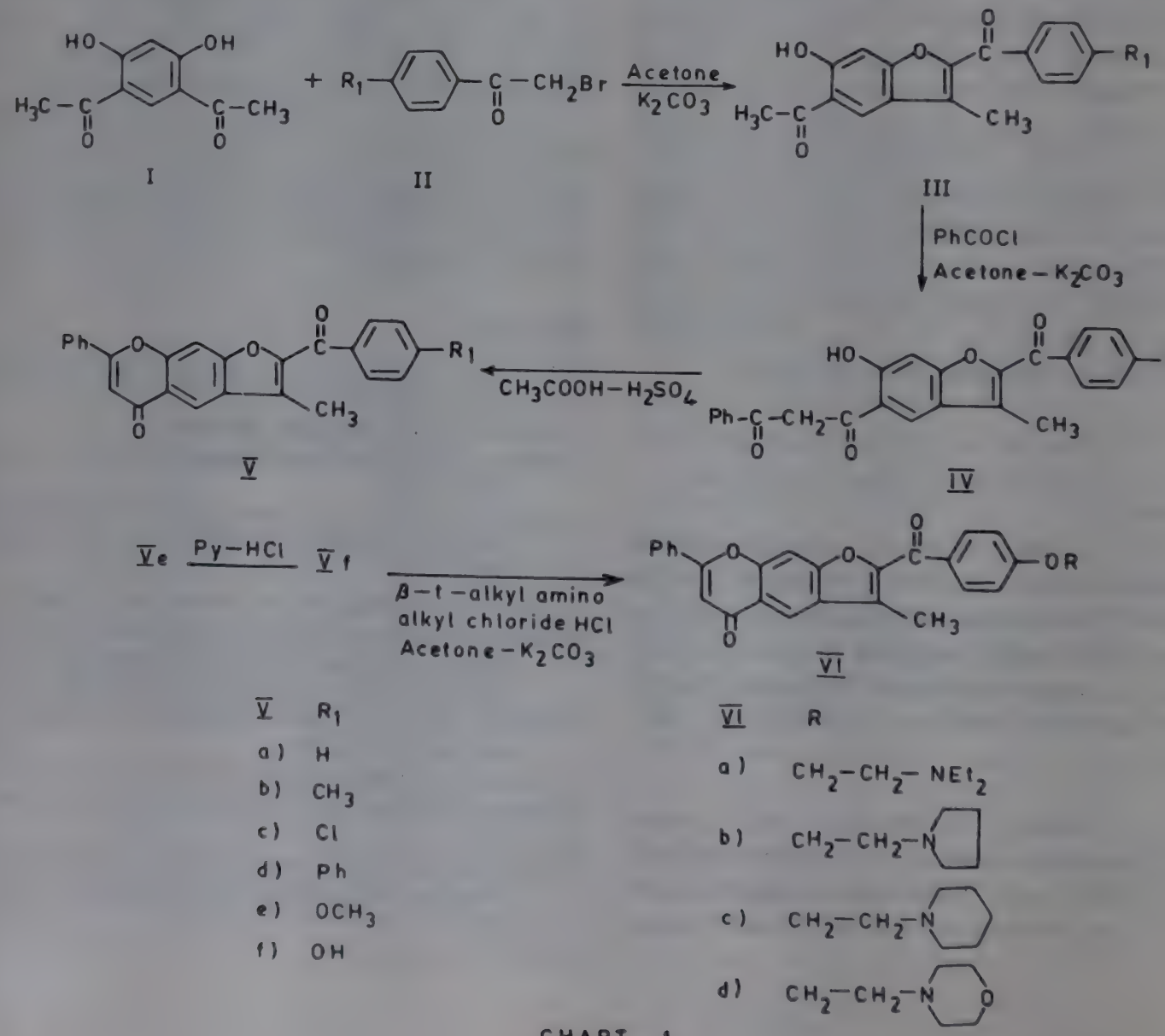

CHART 1

alkoxy)benzoyl]-furanobenzopyrones (VIa-d) were also synthesised to study their antifertility activity. Towards this end Ve was demethylated with pyridine hydrochloride to afford 2-(4-hydroxybenzoyl)-3-methyl-7-phenyl-5*H*-furo[3,2-*g*] [1]benzopyran-5-one (Vf) which on treatment with *β*-*t*-alkylaminoalkyl halide hydrochloride in acetone-potassium carbonate yielded the corresponding 2-[4-(*β*-*t*-alkylaminoalkoxy)benzoyl]-3-methyl-7-phenyl-5*H*-furo[3,2-*g*][1]benzopyran-5-ones (VIa-d, Chart 1).

The structures of all the compounds, given in Table 1, were established by elemental analyses and characteristic spectral data.

The compounds were tested for their antifertility activity and all of them were found to be ineffective as post-coital antifertility agents at a dose of 15 mg/kg.

The preparations detailed in the sequel are typical. All the compounds having a common basic skeleton with differences in substitution pattern were synthesised by a similar procedure.

5-Acetyl-2-benzoyl-6-hydroxy-3-methylbenzofuran (IIIa)

A mixture of resdiacetophenone (I, 0.01 mol) and *ω*-bromoacetophenone (IIa, 0.01 mol), dry acetone (300 ml) and anhydrous potassium carbonate (0.05 mol) was refluxed for 6 hr, filtered, the filtrate concentrated and the residue poured over crushed ice. The solid separated was filtered, washed with water and extracted with hot 5% aqueous sodium hydroxide. The crude product obtained on neutralization of the alkaline solution was crystallised from methanol as yellow needles, yield 80%, m.p. 130°; IR (nujol): 1640, 1600 cm^{-1}; PMR ($CDCl_3$): δ 2.5 (*s*, 3H, C_3-CH_3), 2.6 (*s*, 3H, C_5-H, $-COCH_3$) and 7.8-8.1 (*m*, 3H, $C_{2'6'}$, C_4-H) (Found: C, 73.5; H, 4.8. $C_{18}H_{14}O_4$ requires C, 73.5; H, 4.8%).

2-Benzoyl-5-benzoylacetyl-6-hydroxy-3-methylbenzofuran (IVa)

A mixture containing IIIa (1 g), benzoyl chloride (1.7 ml), potassium carbonate (5 g), and acetone (30 ml) was refluxed for 36 hr. The yellow solid separated was filtered, washed, dried and recrystallised from acetone to furnish IVa as dark yellow needles. It gave reddish brown colour with neutral ferric chloride; yield 70%; m.p. 170 (Found: C, 75.3; H, 4.6. $C_{25}H_{18}O_5$ requires C, 75.4; H, 4.5%).

2-Benzoyl-3-methyl-7-phenyl-5H-furo[3,2-*g*]-[1]*benzopyran-5-one* (Va)

A mixture containing IVa (2 g), acetic acid (19 ml) and conc sulphuric acid (1 ml) was heated on a steam-bath for 30 min, cooled, poured into water, the solid that separated filtered, dried and crystallised from dioxan to afford Va; yield 65%, m.p. 190° (Found: C, 78.8; H, 4.3. $C_{25}H_{16}O_4$ requires C, 78.9; H, 4.2%); IR (nujol): 1630, 1600 cm^{-1}; PMR (DMSO-d_6): δ 2.6 (*s*, 3H, C_3-CH_3), 7.0 (*s*, 1H, C_6-H), 7.4-7.7 (*m*, 6H, C_7-Ph, C_9-H), 7.8-8.2 (*m*, 5H, $-COPh$), 8.5 (*s*, 1H, C_4-H); UV (dioxan): 302 (log ε 4.5) and 346 nm (log ε 4.37).

Table 1—Characterization Data of 2-Aroyl-3-methyl-7-phenyl-5*H*-furo[3,2-*g*][1]benzopyran-5-ones

Compd*	m.p.† (°C)	Mol. formula
Va	190	$C_{25}H_{16}O_4$
Vb	215	$C_{26}H_{18}O_4$
Vc	209	$C_{25}H_{15}O_4Cl$
Vd	218	$C_{31}H_{20}O_4$
Ve	174	$C_{26}H_{18}O_5$
Vf	230	$C_{25}H_{16}O_5$
VIa	165	$C_{31}H_{29}O_5N$
VIb	148	$C_{31}H_{27}O_5N$
VIc	152	$C_{32}H_{29}O_5N$
VId	158	$C_{31}H_{27}O_6N$

*All the compounds were crystallised from dioxane and gave satisfactory elemental analyses
†Melting points are uncorrected.

2-(4-Hydroxybenzoyl)-3-methyl-7-phenyl-5H-furo[3,2-*g*][1]*benzopyran-5-one* (Vf)

Ve (0.03 mol) and freshly distilled pyridine hydrochloride (0.3 mol) were together melted at 220°C over an oil-bath and kept at that temperature for 40 min. The mixture was cooled, triturated with water. The solid separated was filtered, dried and crystallised from dioxan, m.p. 230° (Found: C, 75.6; H, 4.1. $C_{25}H_{16}O_5$ requires C, 75.8; H, 4.0%).

2-[4-(t-Pyrrolidinoethoxy)benzoyl]-3-methyl-7-phenyl-5H-furo[3,2-*g*][1]*benzopyran-5-one* (VIb)

A mixture containing Vf (0.01 mol), N-(2-chloroethyl)-pyrrolidine hydrochloride (0.01 mol) and freshly heated potassium carbonate (0.05 mol) in dry acetone (200 ml) was refluxed for 20-22 hr. At the end of the reaction, acetone was removed by distillation and the residue triturated with water, the solid that separated was filtered, dried and recyrstallised from dioxan to provide title compound; yield 60%, m.p. 165° (Found: C, 77.9; H, 5.6; N, 2.8. $C_{31}H_{27}O_4N$ requires C, 78.0; H, 5.7; N, 2.9%); IR (nujol): 1640, 1600 cm^{-1}; PMR ($DMSOCl_6$): δ 1.2-1.5 (*m*, 4H, $C_{2''}$, $C_{3''}$ protons of pyrrolidine ring), 2.3-2.5 (*m*, 9H, C_3-CH_3 and $-CH_2-N(CH_2)_2$ of pyrrolidine ring), 4.1 (*t*, 2H, $-O-CH_2-$), 6.7-6.9 (*m*, 3H, C_6-H, $C_{5'5}$), 7.4-7.7 (*m*, 6H, C_7-Ph, C_9-H), 7.8-8.0 (*m*, 2H, $C_{2'6'}$) and 8.2 (*s*, 1H, C_4-H); UV (dioxan): 299 (log ε 4.56), 313 (log ε 4.55) and 347 nm (log ε 4.49).

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Antiinflammatory Derivatives of Substituted Propionic Acids—I

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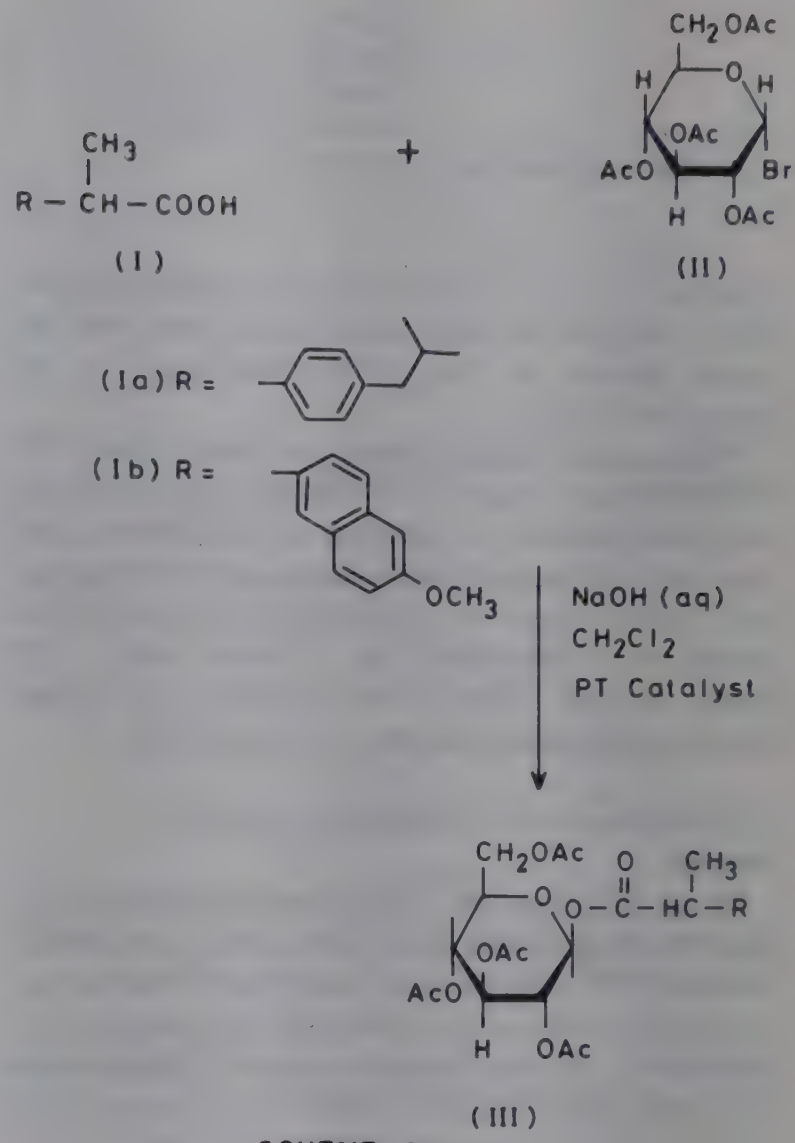
β-Glycosides (IIIa,b) of *d*-Naproxen (Ia) and Ibuprofen (Ib) are prepared by treating peracetylglucosyl bromide with sodium salts of Ia and Ib using phase transfer conditions at room temperature. These compounds are screened for their pharmacological properties.

The propionic acid derivatives are well known for their antiinflammatory activity. Products like *d*-Naproxen, Ibuprofen, Ketoprofen etc. are some of the known drugs of this family. The major problem with these drugs taken either orally or subcutaneously, is gastric ulceration and haemorrhage[1], probably due to systemic as well as topical action. As they are more ulcerogenic when administered orally, the primary insult is due to their inhibition of prostaglandin biosynthesis at mucosa level[2], and the topical insult might be due to local irritation caused by high drug concentration and erosive property of the carboxylic group[3].

We thought of masking this carboxylic group in the form glycosidal derivatives, so as to reduce their gastric ulceration activity and also increase their absorption values. With this in mind, we prepared the glycosides of *d*-Naproxen and Ibuprofen and studied their activity.

Acetylated B-D-glucopyranosides of *d*-Naproxen (Ia) and Ibuprofen (Ib) are synthesised efficiently by treating 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with sodium salts of *d*-Naproxen and Ibuprofen using a phase transfer catalyst[4] in a methylene chloride/water, two-phase system (see Scheme 1). The products (IIIa,b) are isolated by simple aqueous work-up and purification is achieved, without recourse to chromatography, by crystallisation from ethanol. The respective glycosides were obtained in 60% yields. This method of glycosilation is stereoselective easy and has the potentiality of being scaled-up to large scale preparation.

The anomeric configuration of the isolated products have been assigned by PMR spectroscopy. The PMR



SCHEME 1

spectrum of IIIa exhibits a doublet of doublet ($J_{1,2}$ = 7.5 and $J_{1,3}$ = 2 Hz) assignable to H-1 whereas that of IIIb exhibits a doublet ($J_{1,2}$ = 7 Hz), for H-1, thereby confirming β-configuration for the products.

The mass spectra of IIIa,b displayed peaks at *m/z* 331, 211 and 169, which support the presence of glucopyranosyl structure in the molecule.

Antiinflammatory effect of each drug was measured against simultaneously run controls, using the method of Winter *et al*[5]. All the rats, weighing between 100-150 g, were fasted for 48 hr. Drugs were given orally as a suspension in 0.5% methocel. The suspension (3 ml) was administered to each rat. One hour after drug administration, 0.1 ml of 1% carrageenin suspension in saline solution was injected subcutaneously under the planter surface of the hind foot. At 3 hr after carrageenin injection, the volume of paw was measured in a plethysmograph. Edema was measured in a precaliberated plethysmograph as the difference between the volume of the paws measured before and 3 hr after giving carrageenin injection. The results

Table 1—Effect of Drugs on Carrageenin-induced Paw Edema in Rats

No.	Drug	n	Dose mg/kg	Mean paw swelling ± S.E.	Suppression %
1	Control	7	—	0.556 ± 0.086	—
2	Ibuprofen	8	50	0.2185 ± 0.046	60
3	Glucoside of Ibuprofen	7	50	0.196 ± 0.071	64.7
4	Glucoside of *d*-naproxen	7	50	0.271 ± 0.034	51.2

n = number of animals used for each test

presented in Table 1 show that these derivatives are more active than the parent compounds, even when the actual amount of the parent compounds in the derivatives is small.

PMR spectra were recorded on Varian Excell 100 (100 MHz) and Hitachi R 600 (60 MHz) spectrometers and chemical shifts are reported in δ(ppm) with TMS as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 681 spectrophotometer and mass spectra were determined on a Varian MAT 1125 model. Melting points were determined on Veego melting point apparatus and are uncorrected.

2,3,4,6-Tetra-O-acetyl α-D-glucopyranosyl bromides

To a solution of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (20 g) in alcohol-free chloroform (40 ml) was added 30% HBr in acetic acid (25 ml). The mixture was kept at room temperature for 3 hr, poured over crushed ice, the organic layer separated, washed with cold water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude gummy product so obtained was crystallised from ether-hexane, yield 13.8 g (65%), m.p. 88-89°C. It was used immediately for further reaction.

Acetylated β-D-glucopyranoside derivative (IIIa) of d-Naproxen (Ia)

A solution of Ia (2.76 g, 12 mmol) in aq. 10% sodium hydroxide (12 ml, 30 mmol) was stirred vigorously at room temp. Citrimide (0.672 g, 2 mmol) in methylene chloride (20 ml) was added to it and the reaction mixture stirred for 30 min. 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (4.11 g, 10 mmol) in methylene chloride (30 ml) was added to the reaction mixture during 30 min. The two phases were separated and the organic layer washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude gummy product (IIIa) was purified by crystallisation from ethanol, yield 3.4 g (60%), white crystals, m.p. 170-72°, $[\alpha]_D^{25}$ +35° (*c*, 1, $CHCl_3$); IR (nujol): 1760 (acetoxy), 1745 (glycosidal ester) and 1610 cm^{-1} (aromatic); PMR (100 MHz, $CDCl_3$): 1.62 (*d*, J = 7.5 Hz, 3H, CH_3), 1.77 (*s*, 3H, $CO-CH_3$), 2.0 (*s*, 3H, $CO-CH_3$), 2.04 (*s*, 3H, $-CO-CH_3$), 2.05 (*s*, 3H, $-CO-CH_3$) 3.94 (*s*, 3H, $-OCH_3$), 3.7-3.98 (2H, H-5 and H of propionic acid moiety), 4.07 (*dd*, 1H, $J_{6.6}$ = 12 Hz, $J_{6.5}$ = 2 Hz, H-6), 4.15 (*dd*, 1H, $J_{6.6}$ = 12 Hz, $J_{6.5}$ = 6.5 Hz, H-6), 5.02-5.28 (3H, H-2,3,4); 5.75 (*dd*, 1H, $J_{1.2}$ = 7.5 Hz, $J_{1.3}$ = 2 Hz, H-1) and 7.1-7.82 (6H, aromatic); MS: *m/z* 560 (48.1), 331 (23.6), 271 (6.4), 213 (15.5), 211 (16.5), 185 (81.8), 169 (5.8), 157 (14.6), 43 (100) (Found: C, 59.7; H, 5.7. $C_{28}H_{32}O_{12}$ requires C, 60.0; H, 5.7%).

Acetylated β-D-glucopyranoside derivative (IIIb) of Ibuprofen (Ib)

IIIb was synthesised from Ib (2.47 g, 12 mmol) using the above procedure. The product was recrystallised from emthanol as white crystals, yield 3.1 g (60%), m.p. 110-11°, $[\alpha]_D^{25}$ +45° (*c*, 1, $CHCl_3$); IR (nujol): 1740 (acetoxy) 1715 (glycosidal ester), 1600 and 1505 cm^{-1} (aromatic); PMR (60 MHz, $CDCl_3$): 0.9 (*d*, J = 6 Hz, 6H, *gem*-dimethyl), 1.55 (*s*, 3H, $-O-CO-CH_3$), 1.9 (*s*, 3H, $OCO-CH_3$), 2.0 (*s*, 6H, 2-$OCOCH_3$), 2.45 (*d*, J = 6 Hz, 2H, $-CH_2-$ of isobutyl), 3.5-4.0 (*m*, 2H, H-5 & H of propionic acid), 4-4.3 (2H, CH_2, H-6) 5.2 (*bs*) 3H, H-2, 3 and 4), 5.65 (*d*, J = 7.0 Hz, 1H, H-1), 7.09, 7.22 (*d*, 4H, J = 9 Hz, aromatic ortho protons); MS: *m/z* 331 (13.8), 211 (3.5), 189 (6.8), 169 (86.9), 161 (3.6), 133 (0.75), 119 (42), 91 (19.3) and 43 (100) (Found: C, 60.5; H, 6.5. $C_{26}H_{36}O_{11}$ requires C, 59.53, H, 6.91).

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Synthesis of Some Newer 4-(3-Methyl-5-oxo-4-pyrazolidenemethyl)phenoxyacetic Acid Benzylidenehydrazides & α-Methylbenzylidenehydrazides as CNS Active & Antiinflammatory Agents

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The title compounds (IVa-q) have been synthesized and found to be non-toxic and CNS depressant or stimulant. In antiinflammatory activity, these compounds show 4-23% protection against the carrageenin-induced mice paw oedema.

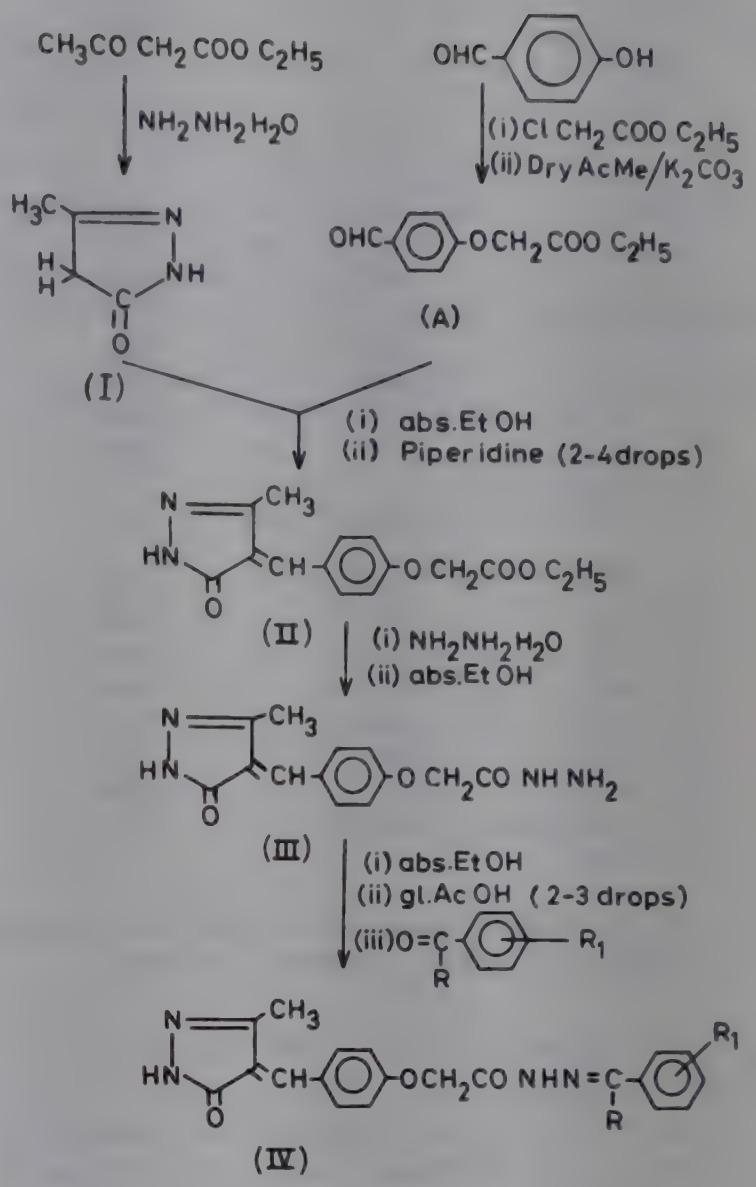
Pyrazole derivatives have been found to be potent antiinflammatory agents[1,2]. Oxopyrazoles are reported to possess analgesic[3], CNS depressant[4] and diverse enzymes inhibitory[5] activities. Phenylbutazone, an oxo-pyrazolidene derivative, is a potent broad spectrum antiinflammatory agent[6]. In view of these reports, the synthesis and evaluation of the gross CNS activity and antiinflammatory activity of the title compounds have been undertaken.

The requires ethyl 4-formylphenoxyethylacetate (**A**) was prepared by condensing 4-formylphenol with ethyl chloroacetate in dry acetone and anhyd. K_2CO_3. The intermediate **A** on condensation with 3-methyl-5-oxopyrazole (I) yielded ethyl 4-(3-methyl-5-oxo-4-pyrazolidenemethyl)phenoxyacetate (II) which on hydrazinolysis furnished 4-(3-methyl-5-oxo-4-pyrazolidenemethyl)phenoxyacetic acid hydrazide (III). The hydrazide III underwent condensation with aryl aldehydes or acetophenones to furnish the title compounds (IV; Table 1). The reaction sequence is shown in Scheme 1.

Structures of all the compounds synthesised were confirmed by elemental analyses (C, H and N), IR and PMR spectra.

Pharmacological screening

All the compounds were screened for their toxicity, CNS and antiinflammatory activities in albino mice. The ALD_{50} values[7] and antiinflammatory activity[8] were determined by standard methods. At 1/5th of ALD_{50}, behavioural changes in spontaneous motor activity (SMA), reactivities to sound and touch (RST)



Scheme 1

writhing, hypothermia and mobility counts (recorded on an actophotometer) were noted. For comparison of antiinflammatory activity, indomethacin, a known drug was used at a concentration of 2mg/kg.

The compounds were found to be nontoxic. In their CNS screening nine compounds (IVa-i) were found to be CNS depressants (12-76%), while eight compounds (IVj-q) were CNS stimulants (8-21%), as they decreased and increased the SMA, RST and mobility counts respectively. Most of compounds also induced writhing and showed hypothermia (0.4-1.6°C). In their antiinflammatory activity, the compounds IVa-q showed 4-23% protection against the carrageenin-induced mice paw oedema, at 1/5th of their ALD_{50}, as compared to 36% protection shown by indomethacin. All the pharmacological data are given in Table 1.

M.ps were taken in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1})

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Table 1—Physical and Pharmacological Data of 4-(3-Methyl-5-oxo-4-pyrazolidenemethyl)phenoxyacetic Acid Benzylidenehydrazides and α-Methylbenzylidenehydrazides (IVa-q)*

Compd	R_1	m.p. °C	Yield (%)	ALD_{50} (mg/kg i.p.)	Gross CNS Observation†					Antiinflammatory activity (% protection)
					SMA & RST	Writhing	Hypothermia (°C)	Depressant activity (%)	Stimulant activity (%)	
					R = H					
IVa	H	232-35	70	1000	d	(−)	1.3	76	(−)	4
IVb	2-OH	240	75	681	d	(−)	1.3	12	(−)	10
IVc	4-OH	228-30	65	>1000	d	(+)	0.4	29	(−)	12
IVd	4-OCH_3	235-40	60	1000	d	(−)	1.5	54	(−)	(−)
IVe	3-NO_2	188-90	55	1000	d	(+)	1.1	44	(−)	5
IVf	4-$N(CH_3)_2$	228-31	55	>1000	d	(+)	0.8	30	(−)	13
IVg	3-OCH_3, 4-OH	232-35	65	>1000	d	(+)	1.3	27	(−)	9
IVh	3,4-$(OCH_3)_2$	235-37	60	>1000	d	(−)	1.2	23	(−)	(−)
IVi	3,4-$(OCH_3)_2$, 6-NO_2	200-05	60	681	d	(+)	1.4	32	(−)	(−)
					R = CH_3					
IVj	H	238-40	70	316	i	(−)	1.2	(−)	19	18
IVk	2-OH	248-50	70	>1000	i	(−)	0.9	(−)	18	20
IVl	4-OH	228-30	75	>1000	i	(−)	0.8	(−)	8	22
IVm	4-CH_3	236-38	75	681	i	(+)	0.8	(−)	12	19
IVn	4-OCH_3	224-26	55	861	i	(+)	1.2	(−)	20	23
IVo	4-NH_2	240-45	50	681	i	(+)	1.6	(−)	21	17
IVp	4-Cl	242-45	75	>1000	i	(+)	1.5	(−)	21	17
IVq	3-NO_2, 4-Br	222-25	80	681	i	(+)	1.3	(−)	9	21
Indomethacin		—	—	—	—	—	—	—	—	36

*Satisfactory C, H and N analyses were obtained for all the compounds.
†d = decreased; i = increased; (−) = absent; (+) = present.

and PMR spectra in $CDCl_3$ or DMSO-d_6 on a Varian A-60D instrument using TMS as internal standard (chemical shift in δ, ppm). Purity of the compounds was checked by TLC on plates coated with silica gel G (0.25 m) using benzene-methanol (95 : 5) as solvent.

Ethyl 4-formylphenoxyacetate (A)

An equimolar (0.1 mol) mixture of 4-formylphenol and ethyl chloroacetate in dry acetone (200 ml) containing anhyd. K_2CO_3 (0.15 mol) was refluxed for 10 hr. Excess solvent was distilled off and the residual mass treated with excess of water. The oily layer separated was extracted with chloroform, dried over fused $CaCl_2$ and chloroform distilled off. The ester obtained was used as such in the next step.

Ethyl 4-(3-methyl)-5-oxo-pyrazolidenemethyl)-phenoxyacetate (II)

A mixture of 3-methyl-5-oxopyrazole[9] (0.1 mol) and A (0.1 mol) in abs. ethanol (200 ml) containing 4 drops of piperidine was refluxed for 4 hr. The solid separated was filtered, washed with ethanol and recrystallised from ethyl acetate, m.p. 180°; yield 95%; IR: 3200 (N − H), 3050, 2900 (C − H), 1750 (C = O ester), 1690 (C = O), 1650 (C = CH), 1630 (C = N); PMR ($CDCl_3$): 8.68 (*s*, 1H, N − H), 7.70-6.76 (*m*, 5H, Ar-*H* and C = CH), 4.45 (*s*, 2H, OCH_2CO), 4.30 (*q*, J = 4.5 Hz, 2H, ester CH_2), 1.4 (*s*, 3H, pyrazole $-CH_3$) and 1.3 (*t*, J = 4.5 Hz, 3H, ester $-CH_3$) (Found: C, 62.6; H, 5.6; N, 9.8. $C_{15}H_{16}N_2O_4$ requires C, 62.5; H, 5.6; N, 9.7%).

4-(3-Methyl-5-oxo-4-ptrazolidenemethyl)-phenoxyacetic acid hydrazide (III)

To a boiling solution of II (0.1 mol) in abs. ethanol (50 ml), hydrazine hydrate (99%, 0.12 mol) was added and resulting solution refluxed for 4 hr. Excess of solvent was distilled off, and the solid, thus obtained filtered washed with water and recrystallised from ethanol, m.p. 215-16°, yield 70%; IR: 3050 (N − H), 3050-2900 (C − H), 1690 (C = O), 1650 (C = CH), 1640 (C = O hydrazide), 1630 (C = N); PMR (DMSO-d_6): 9.60 (*s*, 3H, $CO - NH - NH_2$), 8.70 (*s*, 1H, pyrazol N − H), 7.68-6.76 (*m*, 5H, Ar-*H* and C = CH); 4.46 (*s*, 2H, OCH_2CO) and 1.4 (*s*, 3H, pyrazole CH_3) (Found: C, 57.0; H, 5.1; N, 20.5. $C_{13}H_{14}N_4O_3$ requires C, 56.9; H, 5.1; N, 20.4%).

4-(3-Methyl-5-oxo-4-pyrazolidenemethyl)-phenoxyacetic acid benzylidenehydrazides and α-methylbenzylidenehydrazides (IVa-q; Table 1): *General procedure*

An equimolar (0.005 mol) mixture of III and appropriate aryl aldehyde or acetophenone in dry ethanol (50 ml) containing 2 drops of gl. acetic acid was refluxed for 3 hr. Excess ethanol was distilled off, and the separated solid filtered and recrystallised from dioxane to give IV. The spectral data of IVa as a representative compound are as follow—IR: 3250, (N – H), 3100, 2950 (C – H), 1690 (C = O), 1650 (C = CH), 1640 (NHC = O), 1630, 1620 (C = N); PMR (DMSO-d_6): 9.22 (*s*, 1H, CONH), 8.70 (*s*, 1H, pyrazole N – H), 7.76-6.60 (*m*, 11H, Ar-*H*, N = CH – Ar and C = CH), 4.46 (*s*, 2H, OCH_2CO) & 1.39 (*s*, 3H, pyrazole CH_3).

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Synthesis of N-Aryl/heteroaryl/-substituted-methyl-α-(*p*-substituted anilino)succinimides as Antituberculosis Agents

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A series of N-aryl/heteroaryl/substituted-methyl-α-(*p*-substituted anilino)succinimides (II) have been prepared and screened *in vitro* against $H_{37}Rv$ strain of *Mycobacterium tuberculosis*. Some of these compounds exhibit activity upto 0.39 μg/ml concentration.

Succinimide derivatives are known to possess anticonvulsant[1], fungicidal[2] and antibacterial[3] activities. They also exhibit antituberculosis[4] activity and because of this Twomey suggested their use in the treatment of tuberculosis[5]. Earlier studies carried out in our laboratory have revealed that N-aryl/heteroaryl/substituted-methyl-α-(pyrrolidino/-piperidino)succinimides and N-aryl/heteroaryl/substituted-methyl-α-morpholino/N′-methyl-piperazinyl-succinimides exhibit *in vitro* significant antituberculosis activity[6,7]. This prompted us to synthesize the title compounds and evaluate their possible antituberculosis activity.

The required N-substituted-phenyl, methyl and heteroaryl)maleimides (I; Table 1) were prepared by the usual method[8] and treated with *p*-substituted anilines in an organic solvent to obtain the corresponding N-aryl/heteroaryl/substituted-methyl-α-(*p*-substituted anilino)succinimides (II; Table 2) (Scheme 1).

Antituberculosis activity

Compounds II were screened *in vitro* against $H_{37}Rv$ strain of *M. tuberculosis* by the serial dilution method of Doub and Youmans[9]. Among the succinimides tested, the compounds II_{22}, II_{23}, II_{24} and II_{30} (MIC 0.39 μg/ml; Table 2) were as active as the standard antitubercular drug *p*-aminosalicylic acid (MIC 0.4 μg/ml). Other notably active compounds were II_{14}, II_{18}, II_{19}, II_{20} and II_{21} (MIC 0.78 μg/ml; Table 2). Among the three series of succinimide derivatives synthesized, the N-aryl/heteroaryl/substituted-methyl analogs having *p*-methoxyanilino group at α-position of the succinimide moiety did not show marked antituberculosis activity while the *p*-ethoxyanilino analogs exhibited more significant activity than the *p*-(phenylmercapto)anilino analogs. It is worthwhile to note that the activity was very promising especially in N-heteroaryl/substituted-methyl-α-(*p*-ethoxyanilino-)succinimides than in N-aryl-α-(*p*-ethoxyanilino-)succinimides which indicates that the former groups contributed to the enhancement of activity. The minimum inhibitory concentration (MIC) substantially decreased from compounds bearing *p*-methoxyanilino group to the ones with *p*-ethoxyanilino group while it relatively increased from compounds bearing *p*-ethoxyanilino group to the ones with *p*-(phenylmercapto)anilino group at α-position of

Table 1—Characterization Data of N-(Substituted-phenyl, methyl and heteroaryl)maleimides (I)

Compd	R	Yield (%)	m.p. °C	Mol. formula	Found (%)			Calc. (%)		
					C	H	N	C	H	N
I_1	*o*-Methoxyphenyl	75	115	$C_{11}H_9NO_3$	65.4	4.1	6.7	65.0	4.4	6.9
I_2	*p*-Methylphenyl	83	143	$C_{11}H_9NO_2$	70.2	5.0	7.2	70.6	4.8	7.5
I_3	*p*-Methoxyphenyl	88	147	$C_{11}H_9NO_3$	65.4	4.9	7.2	65.0	4.4	6.9
I_4	*p*-Ethoxyphenyl	89	132	$C_{12}H_{11}NO_3$	66.4	5.3	6.9	66.2	5.1	6.5
I_5	*p*-(*n*-Propoxy)phenyl	85	96	$C_{13}H_{13}NO_3$	67.9	5.5	5.9	67.5	5.6	5.6
I_6	*p*-(*n*-Butoxy)phenyl	80	81	$C_{14}H_{15}NO_3$	68.4	6.0	5.9	68.6	6.1	5.7
I_7	*p*-(Phenylmercapto)phenyl	83	109	$C_{16}H_{11}NO_9S$	68.6	3.7	4.8	68.3	3.9	5.0
I_8	Benzyl	71	92	$C_{11}H_9NO_2$	70.2	5.0	7.1	70.6	4.8	4.4
I_9	β-Phenylethyl	73	112	$C_{12}H_{11}NO_2$	71.5	5.7	6.7	71.6	5.5	7.0
I_{10}	α-Methylbenzyl	78	83	$C_{12}H_{11}NO_2$	71.6	5.8	6.7	71.6	5.5	7.0
I_{11}	α-Methyl-β-phenylethyl	76	97	$C_{13}H_{12}NO_2$	72.8	5.3	6.7	72.6	5.6	6.5
I_{12}	5-Methyl-3-isoxazolyl	76	251	$C_8H_6N_2O_3$	53.8	3.2	15.9	53.9	3.4	15.7

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Table 2—Characterization Data of N-Aryl/heteroaryl/substituted-methyl-α-(*p*-substituted-anilino)succinimides (II)

Compd	R	Yield (%)	m.p. °C	Mol. formula	Found (%)			Calc. (%)			*In vitro* antitubercular activity (μg/ml)*
					C	H	N	C	H	N	
				R′ = Methoxy							
II_1	*o*-Methoxyphenyl	55	58	$C_{18}H_{18}N_2O_4$	66.5	6.4	8.7	66.3	6.3	8.6	6.26
II_2	*p*-Methylphenyl	58	198	$C_{18}H_{18}N_2O_3$	69.6	6.1	9.1	69.7	5.8	8.8	6.25
II_3	*p*-Methoxyphenyl	63	216	$C_{18}H_{18}N_2O_4$	66.7	6.4	8.5	66.3	6.3	8.6	1.56
II_4	*p*-Ethoxyphenyl	59	220	$C_{19}H_{20}N_2O_4$	67.0	5.9	8.7	67.1	5.9	8.2	3.12
II_5	*p*-(*n*-Propoxy)phenyl	60	215	$C_{20}H_{22}N_2O_4$	67.3	6.1	7.9	67.8	6.2	7.7	1.56
II_6	*p*-(*n*-Butoxy)phenyl	61	207	$C_{21}H_{24}N_2O_4$	68.6	6.4	7.8	68.5	6.5	7.6	3.12
II_7	*p*-Phenylmercaptophenyl	56	170	$C_{23}H_{20}N_2O_3S$	68.7	4.8	6.7	68.3	4.9	6.9	12.50
II_8	Benzyl	55	Oil	$C_{18}H_{18}N_2O_3$	69.8	5.6	9.5	69.8	5.8	9.1	3.12
II_9	β-Phenylethyl	50	Oil	$C_{19}H_{20}N_2O_3$	70.1	6.3	8.4	70.4	6.2	8.6	12.5
II_{10}	α-Methylphenyl	53	Oil	$C_{19}H_{20}N_2O_3$	70.1	6.3	8.4	70.4	6.2	8.6	6.25
II_{11}	α-Methyl-β-phenylethyl	50	Oil	$C_{20}H_{21}N_2O_3$	70.8	6.5	8.4	71.0	6.2	8.3	6.25
II_{12}	5-Methyl-3-isoxazolyl	48	Oil	$C_{15}H_{15}N_3O_4$	60.0	4.8	13.9	59.8	5.0	13.9	6.25
				R′ = Ethoxy							
II_{13}	*o*-Methoxyphenyl	54	64	$C_{19}H_{20}N_2O_4$	67.0	5.6	8.5	67.1	5.9	8.2	1.56
II_{14}	*p*-Methylphenyl	58	204	$C_{19}H_{20}N_2O_3$	70.6	6.7	8.5	70.4	6.2	8.4	0.78
II_{15}	*p*-Methoxyphenyl	60	207	$C_{19}H_{20}N_2O_4$	67.0	6.1	8.4	67.1	5.9	8.2	1.56
II_{16}	*p*-Ethoxyphenyl	59	225	$C_{20}H_{22}N_2O_4$	69.0	6.2	7.7	69.3	6.2	7.9	6.25
II_{17}	*p*-(*n*-Propoxy)phenyl	58	238	$C_{21}H_{24}N_2O_4$	68.1	6.7	7.4	68.4	6.5	7.6	1.56
II_{18}	*p*-(n-Butoxy)phenyl	64	242	$C_{22}H_{26}N_2O_4$	69.4	6.7	7.1	69.1	6.8	7.3	0.78
II_{19}	*p*-Phenylmercaptophenyl	58	182	$C_{24}H_{22}N_2O_3S$	68.8	5.5	6.9	68.8	5.3	6.7	0.78
II_{20}	Benzyl	58	Oil	$C_{19}H_{20}N_2O_3$	70.0	6.4	8.4	70.4	6.2	8.6	0.78
II_{21}	β-Phenylethyl	52	Oil	$C_{20}H_{22}N_2O_3$	70.6	6.8	8.0	71.0	6.5	8.3	1.56
II_{22}	α-Methylbenzyl	50	Oil	$C_{20}H_{22}N_2O_3$	71.2	6.7	8.2	71.0	6.5	8.3	0.39
II_{23}	α-Methyl-β-phenylethyl	47	Oil	$C_{21}H_{23}N_2O_3$	71.8	6.3	7.7	71.6	6.5	8.0	0.39
II_{24}	5-Methyl-3-isoxazolyl	53	Oil	$C_{16}H_{17}N_3O_4$	61.2	5.2	13.2	61.0	5.4	13.3	0.39
				R′ = *p*-(Phenylmercapto)							
II_{25}	*o*-Methoxyphenyl	60	77	$C_{23}H_{20}N_2O_3S$	67.9	5.1	6.8	68.2	5.0	6.9	3.12
II_{26}	*p*-Methylphenyl	59	83	$C_{23}H_{20}N_2O_3S$	68.1	4.8	6.9	67.9	5.1	7.2	0.78
II_{27}	*p*-Methoxyphenyl	59	80	$C_{23}H_{20}N_2O_3S$	68.1	5.2	6.6	68.2	5.0	6.9	3.12
II_{28}	*p*-Ethoxyphenyl	57	180	$C_{24}H_{22}N_2O_3S$	68.7	5.5	6.6	68.9	5.3	6.7	6.25
II_{29}	*p*-(*n*-Propoxy)phenyl	55	88	$C_{25}H_{24}N_2O_3S$	69.7	5.3	6.6	69.4	5.6	6.5	3.12
II_{30}	*p*-(*n*-Butoxy)phenyl	58	72	$C_{26}H_{26}N_2O_3S$	69.5	6.0	6.1	69.9	5.8	6.3	0.39
II_{31}	*p*-Phenylmercaptophenyl	55	91	$C_{28}H_{22}N_2O_3S_2$	69.4	4.7	5.7	69.7	4.6	5.8	1.56
II_{32}	Benzyl	48	Oil	$C_{23}H_{20}N_2O_2S$	70.8	5.4	7.0	71.0	5.2	7.2	1.56
II_{33}	β-Phenylethyl	48	Oil	$C_{24}H_{22}N_2O_2S$	72.0	5.1	6.7	71.6	5.4	6.9	3.12
II_{34}	α-Methylbenzyl	49	Oil	$C_{24}H_{22}N_2O_2S$	72.0	5.2	7.2	71.6	5.2	6.9	1.56
II_{35}	α-Methyl-β-phenylethyl	49	Oil	$C_{25}H_{23}N_2O_2S$	71.8	5.8	7.0	72.1	5.5	6.7	6.25
II_{36}	5-Methyl-3-isoxazolyl	51	Oil	$C_{20}H_{17}N_3O_3S$	63.0	4.6	11.3	63.3	4.5	11.1	6.25

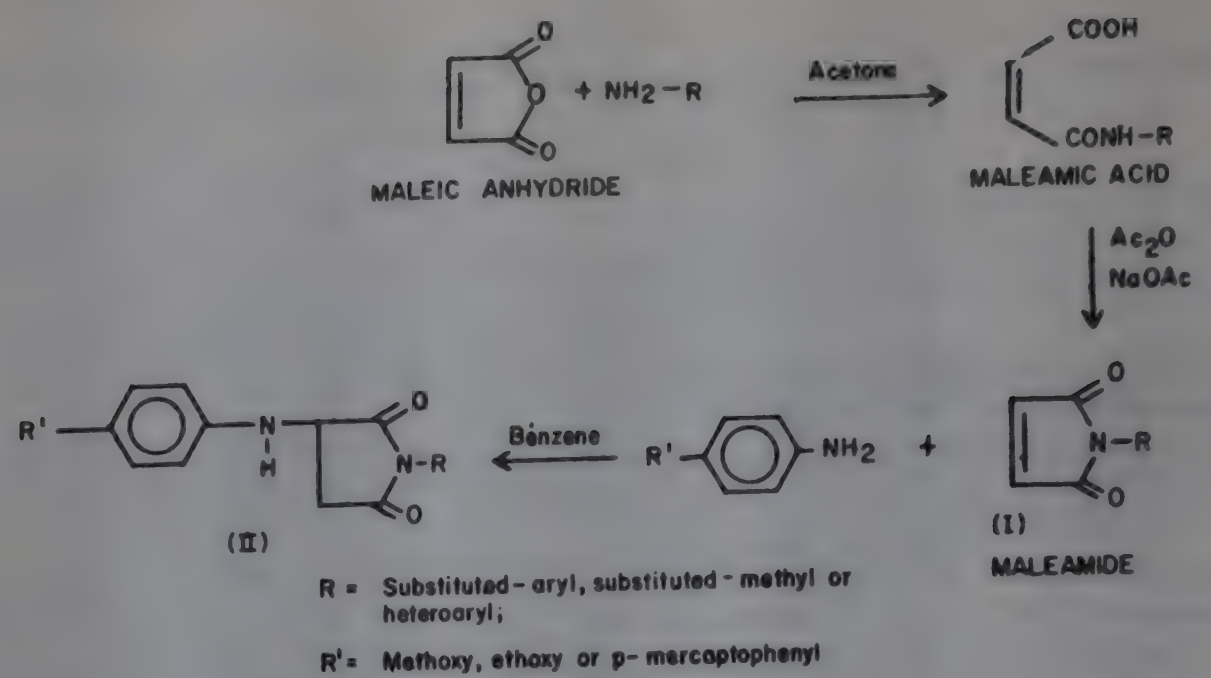
*Standard drugs used were Isoniazide (MIC = 0.04 μg/ml) and *p*-aminosalicylic acid (MIC = 0.4 μg/ml).

the succinimide moiety which implies that *p*-ethoxyanilino group imparts activity. Among the title compounds and the structurally related compounds, studied earlier[6,7] for antituberculosis activity, it can be observed that the title compounds were comparatively more active than the ones studied earlier. This notable increase in activity of some of the title compounds is due to the alteration of groups present at α-position of the succinimide moiety.

Melting points were taken in open capillary tubes and are uncorrected. Purity of the oily compounds was checked by TLC on silica gel using chloroform-methanol (99.5 : 0.5) as irrigant.

N-(p-n-Butoxyphenyl)maleimide (I_1 : *Table* 1)

To a solution of maleic anhydride (7.5 g; 0.076 mol) in dry acetone (50 ml), *p*-(*n*-butoxy)aniline (12.6 g; 0.076 mol) was added at room temperature with stirring in the absence of moisture. The resultant *p*-(*n*-butoxy)phenylmaleamic acid which separated out within 1 hr was filtered, washed with dry acetone, dried and a portion of it (16.5 g; 0.063 mol) heated with anhyd. sodium acetate (1.99 g; 0.023 mol) and acetic



SCHEME 1

anhydride (20.4 g; 0.02 mol; 18.9 mol) at 90° for 2 hr. The reaction mixture was poured on crushed ice, and the separated solid filtered, washed with water, dried and crystallised from ethanol to give pure I_6, yield 12.3 g (80%).

Similarly, all other compounds of the type I reported in Table 1 were prepared.

N-(p-n-Butoxyphenyl)-α-(p-methoxyanilino)-succinimide (II$_6$; Table 2)

p-Anisidine (0.30 g; 0.00245 mol) was added at room temperature to a solution of I_6 (0.57 g; 0.00235 mol) in dry benzene (25 ml) and kept at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue crystallized from ethanol to obtain pure II_6, yield 0.53 g (61.4%).

Similarly, all other members of the series II were prepared and their characterization data are given in Table 2.

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Synthesis & Anthelmintic Activity of Some Carbamates, Thiocarbamates & Ureas Derived from 6-Carboxy-5(*H*)-oxothiazolo[3,2-*a*]pyrimidine†

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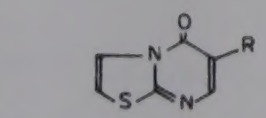
Some new carbamates, thiocarbamates and ureas derived from 6-carboxy-5(*H*)-oxothiazolo[3,2-*a*]pyrimidine have been synthesised and evaluated for their anthelmintic activity.

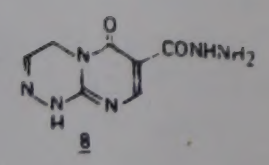
Earlier publications from these laboratories reported the synthesis and anthelmintic activity of certain benzofuran[1], imidazobenzoxazine[2] and purinyl[3] carbamates. In continuation of this work we report in this note the synthesis and anthelmintic activity of some new carbamates, thiocarbamates and ureas derived from 6-carboxy-5(*H*)-oxothiazolo[3,2-*a*]pyrimidine (**2**).

The starting **2** was prepared by the cyclocondensation of 2-aminothiazole with diethyl ethoxymethylenemalonate in refluxing acetic acid followed by hydrolysis of the resultant thiazolopyrimidine ester (**1**) with boiling dil HCl following the reported method[4]. The acid chloride (**3**) of **2** failed to react with NaN_3 under different reaction conditions to give the desired intermediate **4**. Alternatively it was proposed to synthesise **4** by the reaction of the hydrazide (**7**) with HNO_2. Conventional hydrazinolysis[5] of **1** instead of affording the **7**, surprisingly led to the formation of pyrimidinotriazine hydrazide (**8**) presumably through the initial opening of the thiazole ring in **1** with hydrazine followed by recyclisation with the elimination of H_2S. Although **8** has been reported in literature, its characterization data [m.p. $>330°$; IR (nujol): 3300 and 3200 (NH) and 1680 and 1660 (C=O) cm^{-1}; PMR (TFA): δ 4.4 (br*s*, 2H, $-CH_2-$), 7.17 (br *s*, 1H, C_3-H), 8.87 (*s*, 1H, C_8-H); MS: *m/z* 208 (M^+)] have not been reported so far.

Finally **7** was synthesised successfully, albeit in low yield, from *t*-butoxycarbonyl hydrazide (**6**) by treatment with perchloric acid which in turn was obtained by the reaction of **3** with *t*-butyl carbazate. The hydrazide (**7**) on treatment with HNO_2 gave the impure azide (**4**) in low yield. However, it was obtained in excellent yield (80%) by the interaction of **2** with diphenyl phosphoroazidate in refluxing benzene in the presence of triethylamine[6]. Curtius rearrangement of **4** in refluxing benzene gave the isocyanate (**5**) which on reaction *in situ* with various alcohols, thiols and amines furnished the targetted carbamates (**9-14**), S-alkyl/aryl thiocarbamates (**15-17**) and ureas (**18-28**) respectively in good yields (55-70%).



1. R=CO_2Et
2. R=CO_2H
3. R=COCl
4. R=CON_3
5. R= N=C=O
6. R= $CONHNHCO_2Bu$ (t)
7. R= $CONHNH_2$



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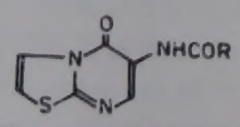

	R
9	OCH_3
10	OC_2H_5
11	OC_3H_7 (n)
12	OC_3H_7 (i)
13	$OCH_2CH_2OCH_3$
14	OC_6H_5
15	SC_3H_7 (n)
16	SC_4H_9 (n)
17	SC_6H_5
18	
19	
20	

	R
21	
22	
23	
24	
25	
26	
27	
28	

The structures of all the new compounds (Table 1), thus synthesised, were established on the basis of their mode of preparation, correct elemental analyses, IR and PMR spectra which were further supported by the mass spectra of a few representative compounds.

Compounds **6**, **7** and **9-28** were tested for their anthelmintic activity against *Nematospiroides dubius* and *Hymenolepis nana* at 1×500 mg/kg (p.o.) dose in mice. They were also tested against *Nippostrongyles brasiliensis* in rats at 3×250 mg/kg (p.o.) dose and *Ancylostoma ceylanicum* at a dose of 2×250 mg/kg (p.o.) in golden hamsters as described earlier[7]. Compounds **19**, **22** and **21** exhibited 30%, 40% and 48% deparasitization respectively of *N. dubius* while **28**, **25** and **18** exhibited low order of activity against *N. brasiliensis* causing 30%, 34% and 37% wormload reduction. None of the compounds reported herein

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showed any significant anthelmintic activity against *H. nana* and *A. ceylanicum*.

Melting points were determined in open capillaries using Gallankamp melting point apparatus and are uncorrected.

t-Butyl-3-[5(*H*)-*oxothiazolo*[3,2-*a*]*pyrimidine*-6-*carbonyl*]*carbazate* (**6**)

To a cooled (0°) and stirred suspension of the acid chloride **3** from **2** [prepared by refluxing for 4 hr **2** (3.92 g) and $SOCl_2$ (20 ml)] in dry pyridine (30 ml) was added *t*-butyl carbazate (2.64 g, 0.02 mol) in two lots during 15 min. After 2 hr at 0° the reaction mixture was further stirred for 4 hr at room temperature. The crude product obtained on evaporation of the resulting solution, was washed with water, dried and crystallized from DMF to give pure **6** (3.1 g, 50%) as colourless needles, m.p. 245°; IR (nujol): 3240 (NH), 1720 (carbazate C=O) and 1660 (amide C=O) cm^{-1}; PMR (TFA): δ 1.67 (*s*, 9H, $-CMe_3$), 7.7 (*d*, J=4.6 Hz, 1H, thiazole proton), 8.2 (*d*, J=4.6 Hz, 1H, thiazole proton), 8.8 (*s*, 1H, C_7-H); MS: *m/z* 310 (M^+) (Found: C, 46.6; H, 4.8; N, 18.0. $C_{12}H_{14}N_4O_4S$ requires C, 46.5; H, 4.5; N, 18.1%).

5(*H*)-*Oxothiazolo*[3,2-*a*]*pyrimidine*-6-*carbohydrazide* (**7**)

The carbazate (**6**, 6.2 g, 0.02 mol) was added in one lot with stirring to 70% $HClO_4$ (15 ml) maintained at 0°. After initial frothing the entire reaction mixture was converted into a thick viscous syrup which was stirred for 10 min at 0° with saturated aq. $NaHCO_3$ (500 ml). The solid, obtained, was filtered off and crystallized from ethanol to give pure **7** (1.26 g, 30%) as pale yellow crystals, m.p. 230°; IR (nujol): 3300 (NH) and 1670 (C=O) cm^{-1}; PMR (TFA): δ 7.7 (*d*, J=4.6 Hz, 1H, thiazole proton), 8.2 (*d*, J=4.6 Hz, 1H, thiazole proton), 8.83 (*s*, 1H, C_7-H); MS: *m/z* 210 (M^+) (Found: C, 40.3; H, 2.7; N, 27.0. $C_7H_6N_4O_2S$ requires C, 40.0; H, 2.9; N, 26.7%).

Methyl 5(*H*)-*oxothiazolo*[3,2-*a*]*pyrimidine*-6-*carbamate* (**9**)

A solution of **2** (3.92 g, 0.02 mol), diphenyl phosphoroazidate (5.50 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in dry benzene (60 ml) was refluxed for 3 hr. The above solution, containing the isocyanate (**5**) formed *in situ*, was cooled to room temperature, treated with methanol (20 ml) and the resulting solution refluxed for 10 hr. It was evaporated to dryness to leave a gummy residue which was extracted with chloroform. The chloroform extract was successively washed with dil.HCl, water, aq. $NaHCO_3$ and water. Evaporation of the dried organic extract followed by crystallization of the residue from chloroform-hexane gave pure **9** (2.7 g, 60%) as colourless needles, m.p. 206°; IR (nujol): 3360 (NH), 1725 (carbamate C=O) and 1660 (amide C=O) cm^{-1} PMR (TFA): δ 3.5 (*s*, 3H, $COOCH_3$), 7.2 (*d*, J=4.5 Hz, 1H, thiazole proton), 7.7 (*d*, J=4.5 Hz, 1H, thiazole proton), 8.6 (*s*, 1H, C_7-H); MS: *m/z* 225 (M^+) (Found: C, 43.0; H, 3.4; N, 18.7. $C_8H_7N_3O_3S$ requires C, 42.7; H, 3.1; N, 18.7%).

The carbamates (**10-14**) and the S-alkyl/aryl thiocarbamates (**15-17**) were prepared in a similar manner by reacting the isocyanate (**5**) with appropriate alcohol, phenol or thiol while the ureas (**18-28**) were obtained by treating **5** with the appropriate amine in refluxing benzene.

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